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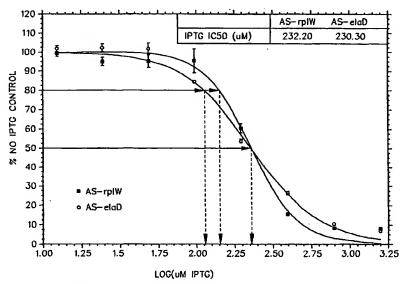
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[Continued on next page]

(54) Title: GENES IDENTIFIED AS REQUIRED FOR PROLIFERATION OF E. COLI



(57) Abstract: The sequences of nucleic acids encoding proteins required for E. coli proliferation are disclosed. The nucleic acids can also be used to screen for homologous genes that are required for proliferation in microorganisms other than E. coli. The nucleic acids can also be used to design expression vectors and secretion vectors. The nucleic acids can be used to express proteins or portions thereof, to obtain antibodies capable of specifically binding to the expressed proteins, and to use those expressed proteins as a screen to isolate candidate molecules for rational drug discovery programs. The nucleic acids of the present invention can also be used in various assay systems to screen for antimicrobial agents.

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GENES IDENTIFIED AS REQUIRED FOR PROLIFERATION OF E. COLI

BACKGROUND OF THE INVENTION

Since the discovery of penicillin, the use of antibiotics to treat the ravages of bacterial infections has saved millions of lives. With the advent of these "miracle drugs," for a time it was popularly believed that humanity might, once and for all, be saved from the scourge of bacterial infections. In fact, during the 1980s and early 1990s, many large pharmaceutical companies cut back or eliminated antibiotics research and development. They believed that infectious disease caused by bacteria finally had been conquered and that markets for new drugs were limited. Unfortunately, this belief was overly optimistic.

The tide is beginning to turn in favor of the bacteria as reports of drug resistant bacteria become more frequent. The United States Centers for Disease Control announced that one of the most powerful known antibiotics, vancomycin, was unable to treat an infection of the common Staphylococcus aureus (staph). This organism is commonly found in our environment and is responsible for many nosocomial infections. The import of this announcement becomes clear when one considers that vancomycin was used for years to treat infections caused by stubborn strains of bacteria, like staph. In short, the bacteria are becoming resistant to our most powerful antibiotics. If this trend continues, it is conceivable that we will return to a time when what are presently considered minor bacterial infections are fatal diseases.

There are a number of causes for the predicament in which practitioners of medical arts find themselves. Over-prescription and improper prescription habits by some physicians have caused an indiscriminate increase in the availability of antibiotics to the public. The patient is also partly responsible, for even in instances where an antibiotic is the appropriate treatment, patients will often improperly use the drug, the result being yet another population of bacteria that is resistant, in whole or in part, to traditional antibiotics.

The bacterial scourges that have haunted humanity remain, in spite of the development of modern scientific practices to deal with the diseases that they cause. Drug resistant bacteria are now advancing on the health of humanity. A new generation of antibiotics to once again deal with the pending health threat that bacteria present is required.

Discovery of New Antibiotics

As more and more bacterial strains become resistant to the panel of available antibiotics, new compounds are required. In the past, practitioners of pharmacology would have to rely upon traditional methods of drug discovery to generate novel, safe and efficacious compounds for the treatment of disease. Traditional drug discovery methods involve blindly testing potential drug candidate-molecules, often selected at random, in the hope that one might prove to be an effective treatment for some disease. The process is painstaking and laborious, with no guarantee of success. Today, the average cost to discover and develop a new drug is nearly US \$500 million, and the

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average time is 15 years from laboratory to patient. Improving this process, even incrementally, would represent a huge advance in the generation of novel antimicrobial agents.

Newly emerging practices in drug discovery utilize a number of biochemical techniques to provide for directed approaches to creating new drugs, rather than discovering them at random. For example, gene sequences and proteins encoded thereby that are required for the proliferation of an organism make for excellent targets since exposure of bacteria to compounds active against these targets would result in the inactivation of the organism. Once a target is identified, biochemical analysis of that target can be used to discover or to design molecules that interact with and alter the functions of the target. Using physical and computational techniques, to analyze structural and biochemical targets in order to derive compounds that interact with a target is called rational drug design and offers great future potential. Thus, emerging drug discovery practices use molecular modeling techniques, combinatorial chemistry approaches, and other means to produce and screen and/or design large numbers of candidate compounds.

Nevertheless, while this approach to drug discovery is clearly the way of the future, problems remain. For example, the initial step of identifying molecular targets for investigation can be an extremely time consuming task. It may also be difficult to design molecules that interact with the target by using computer modeling techniques. Furthermore, in cases where the function of the target is not known or is poorly understood, it may be difficult to design assays to detect molecules that interact with and alter the functions of the target. To improve the rate of novel drug discovery and development, methods of identifying important molecular targets in pathogenic microorganisms and methods for identifying molecules that interact with and alter the functions of such molecular targets are urgently required.

Escherichia coli represents an excellent model system to understand bacterial biochemistry and physiology. The estimated 4288 genes scattered along the 4.6 x 10⁶ base pairs of the Escherichia coli (E. coli) chromosome offer tremendous promise for the understanding of bacterial biochemical processes. In turn, this knowledge will assist in the development of new tools for the diagnosis and treatment of bacteria-caused human disease. The entire E. coli genome has been sequenced, and this body of information holds a tremendous potential for application to the discovery and development of new antibiotic compounds. Yet, in spite of this accomplishment, the general functions or roles of many of these genes are still unknown. For example, the total number of proliferation-required genes contained within the E. coli genome is unknown, but has been variously estimated at around 200 to 700 (Armstrong, K.A. and Fan, D.P. Essential Genes in the metB-malB Region of Escherichia coli K12, 1975, J. Bacteriol. 126: 48-55).

Novel, safe and effective antimicrobial compounds are needed in view of the rapid rise of antibiotic resistant microorganisms. However, prior to this invention, the characterization of even a single bacterial gene was a painstaking process, requiring years of effort. Accordingly, there is an urgent need for more novel methods to identify and characterize bacterial genomic sequences that

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encode gene products required for proliferation and for methods to identify molecules that interact with and alter the functions of such genes and gene products.

SUMMARY OF THE INVENTION

One embodiment of the present invention is a purified or isolated nucleic acid sequence consisting essentially of one of the sequence of nucleotides of SEQ ID NOs: 1-93, wherein expression of said nucleic acid in a microorganism is capable of inhibiting the proliferation of a microorganism. The nucleic acid sequence may have as sequence of nucleotides complementary to at least a portion of the nucleotide sequence of the coding strand of a gene whose expression is required for proliferation of a microorganism. The nucleic acid may have a nucleotide sequence complementary to at least a portion of the nucleotide sequence of an RNA required for proliferation of a microorganism. The nucleotide sequence of the RNA may encode more than one gene product.

Another embodiment of the present invention is a purified or isolated nucleic acid comprising a fragment of one of the nucleotide sequences of SEQ ID NOs.: 1-93, said fragment selected from the group consisting of fragments comprising at least 10, at least 20, at least 25, at least 30, at least 50 and more than 50 consecutive nucleotides of the nucleotide sequence of one of SEQ ID NOs: 1-93.

Another embodiment of the present invention is a vector comprising a promoter operably linked to the nucleic acid sequences of each of the preceding paragraphs. The promoter may be active in a microorganism selected from the group consisting of Aspergillus fumigatus, Bacillus anthracis, Burkholderia cepacia, Campylobacter jejuni, Candida albicans, Candida glabrata (also called Torulopsis glabrata), Candida tropicalis, Candida parapsilosis, Candida guilliermondii, Candida krusei, Candida kefyr (also called Candida pseudotropicalis), Candida dubliniensis, Chlamydia pneumoniae, Chlamydia trachomatus, Clostridium botulinum, Clostridium difficile, Cryptococcus neoformans, Enterobacter cloacae, Enterococcus faecalis, Escherichia coli, Haemophilus influenzae, Helicobacter pylori, Klebsiella pneumoniae, Listeria monocytogenes, Mycobacterium leprae, Mycobacterium tuberculosis, Neisseria gonorrhoeae, Pseudomonas aeruginosa, Salmonella cholerasuis, Salmonella enterica, Salmonella paratyphi, Salmonella typhi, Salmonella typhimurium, Staphylococcus aureus, Klebsiella pneumoniae, Listeria monocytogenes, Moxarella catarrhalis, Shigella boydii, Shigella dysenteriae, Shigella flexneri, Shigella sonnei, Pseudomonas aeruginosa, Staphylococcus epidermidis, Streptococcus pneumoniae, Treponema pallidum, Yersinia pestis and any species falling within the genera of any of the above species.

Another embodiment of the present invention is a host cell containing the vectors of the preceding paragraph.

Another embodiment of the present invention is a purified or isolated nucleic acid consisting essentially of the coding sequence of one of SEQ ID NOs: 106-112, 119-122, 134-160, 164-171, 179-265, 271-273, 275, and 279-286.

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Another embodiment of the present invention is a fragment of the nucleic acid of the preceding paragraph, said fragment comprising at least 10, at least 20, at least 25, at least 30, at least 50 or more than 50 consecutive nucleotides of one of SEQ ID NOs: 106-112, 119-122, 134-160, 164-171, 179-265, 271-273, 275, and 279-286.

Another embodiment of the present invention is a vector comprising a promoter operably linked to the nucleic acid of the preceding two paragraphs.

Another embodiment of the present invention is a purified or isolated antisense nucleic acid comprising a nucleic acid sequence complementary to at least a portion of an intragenic sequence, intergenic sequence, sequences spanning at least a portion of two or more genes, 5' noncoding region, or 3' noncoding region within an operon comprising a proliferation-required gene whose activity or expression is inhibited by an antisense nucleic acid comprising one of SEQ ID NOs.: 1-93.

Another embodiment of the present invention is a purified or isolated nucleic acid comprising a nucleic acid having at least 70% identity to a sequence selected from the group consisting of SEQ ID NOs.: 1-93, fragments comprising at least 25 consecutive nucleotides of SEQ ID NOs.: 1-93, the sequences complementary to SEQ ID NOs.: 1-93 and the sequences complementary to fragments comprising at least 25 consecutive nucleotides of SEQ ID NOs.: 1-93 as determined using BLASTN version 2.0 with the default parameters. The nucleic acid may be from an organism selected from the group consisting of Aspergillus fumigatus, Bacillus anthracis, Burkholderia cepacia, Campylobacter jejuni, Candida albicans, Candida glabrata (also called Torulopsis glabrata), Candida tropicalis, Candida parapsilosis, Candida guilliermondii, Candida krusei, Candida kefyr (also called Candida pseudotropicalis), Candida dubliniensis, Chlamydia pneumoniae, Chlamydia trachomatus, Clostridium botulinum, Clostridium difficile, Cryptococcus neoformans, Enterobacter cloacae, Enterococcus faecalis, Escherichia coli, Haemophilus influenzae, Helicobacter pylori, Klebsiella pneumoniae, Listeria monocytogenes, Mycobacterium leprae, Mycobacterium tuberculosis, Neisseria gonorrhoeae, Pseudomonas aeruginosa, Salmonella cholerasuis, Salmonella enterica, Salmonella paratyphi, Salmonella typhi, Salmonella typhimurium, Staphylococcus aureus, Klebsiella pneumoniae, Listeria monocytogenes, Moxarella catarrhalis, Shigella boydii, Shigella dysenteriae, Shigella flexneri, Shigella sonnei, Pseudomonas aeruginosa, Staphylococcus epidermidis, Streptococcus pneumoniae, Treponema pallidum, Yersinia pestis and any species falling within the genera of any of the above species.

Another embodiment of the present invention is a vector comprising a promoter operably linked to a nucleic acid encoding a polypeptide whose expression is inhibited by an antisense nucleic acid comprising one of SEQ ID NOs.: 1-93. The polypeptide may comprise a polypeptide comprising a sequence selected from the group consisting of SEQ ID NOs: 299-305, 312-315, 327-353, 357-364, 372-458, 464-466, 468 and 472-479.

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Another embodiment of the present invention is a host cell containing the vector of the preceding paragraph.

Another embodiment of the present invention is a purified or isolated polypeptide comprising a polypeptide whose expression is inhibited by an antisense nucleic acid comprising one of SEQ ID NOs.: 1-93, or a fragment selected from the group consisting of fragments comprising at least 5, at least 10, at least 20, at least 30, at least 40, at least 50, at least 60 or more than 60 consecutive amino acids of one of the said polypeptides. The polypeptide may comprise a polypeptide comprising one of SEQ ID NOs.: 299-305, 312-315, 327-353, 357-364, 372-458, 464-466, 468 and 472-479 or a fragment comprising at least 5, at least 10, at least 20, at least 30, at least 40, at least 50, at least 60 or more than 60 consecutive amino acids of a polypeptide comprising a sequence selected from the group consisting of SEQ ID NOs.: 299-305, 312-315, 327-353, 357-364, 372-458, 464-466, 468 and 472-479.

Another embodiment of the present invention is a purified or isolated polypeptide comprising a polypeptide having at least 25% identity to a polypeptide whose expression is inhibited by a sequence selected from the group consisting of SEQ ID NOs.: 1-93, or at least 25% identity to a fragment comprising at least 5, at least 10, at least 20, at least 30, at least 40, at least 50, at least 60 or more than 60 consecutive amino acids of a polypeptide whose expression is inhibited by a nucleic acid selected from the group consisting of SEQ ID NOs.: 1-93 as determined using FASTA version 3.0t78 with the default parameters. The polypeptide may have at least 25% identity to a polypeptide comprising one of SEQ ID NOs: 299-305, 312-315, 327-353, 357-364, 372-458, 464-466, 468 and 472-479 or at least 25% identity to a fragment comprising at least 5, at least 10, at least 20, at least 30, at least 40, at least 50, at least 60 or more than 60 consecutive amino acids of a polypeptide comprising one of SEQ ID NOs.: 299-305, 312-315, 327-353, 357-364, 372-458, 464-466, 468 and 472-479 as determined using FASTA version 3.0t78 with the default parameters.

Another embodiment of the present invention is an antibody capable of specifically binding one of the polypeptides of the preceding paragraph.

Another embodiment of the present invention is a method of producing a polypeptide, comprising introducing a vector comprising a promoter operably linked to a nucleic acid encoding a polypeptide whose expression is inhibited by an antisense nucleic acid comprising one of SEQ ID NOs.: 1-93 into a cell and expressing said polypeptide. The method may further comprise the step of isolating said polypeptide. The polypeptide may comprise a sequence selected from the group consisting of SEQ ID NOs.: 299-305, 312-315, 327-353, 357-364, 372-458, 464-466, 468 and 472-479.

Another embodiment of the present invention is a method of inhibiting proliferation of a microorganism comprising inhibiting the activity or reducing the amount of a gene product whose expression is inhibited by an antisense nucleic acid comprising a sequence selected from the group

consisting of SEQ ID NOs.: 1-93 or inhibiting the activity or reducing the amount of a nucleic acid encoding said gene product. The gene product may comprise a polypeptide comprising a sequence selected from the group consisting of SEQ ID NOs.: 299-305, 312-315, 327-353, 357-364, 372-458, 464-466, 468 and 472-479.

Another embodiment of the present invention is a method for identifying a compound which influences the activity of a gene product required for proliferation, said gene product comprising a gene product whose expression is inhibited by an antisense nucleic acid comprising a sequence selected from the group consisting of SEQ ID NOs.: 1-93, said method comprising contacting said gene product with a candidate compound and determining whether said compound influences the activity of said gene product. The gene product may be a polypeptide and said activity may be an enzymatic activity. The gene product may be a polypeptide and said activity may be a carbon compound catabolism activity. The gene product may be a polypeptide and said activity may be a biosynthetic activity. The gene product may be a polypeptide and said activity may be a transporter activity. The gene product may be a polypeptide and said activity may be a transcriptional activity. The gene product may be a polypeptide and said activity may be a DNA replication activity. The gene product may be a polypeptide and said activity my be a cell division activity. The gene product may be a polypeptide comprising a sequence selected from the group consisting of SEQ ID NOs.: 299-305, 312-315, 327-353, 357-364, 372-458, 464-466, 468 and 472-479.

Another embodiment of the present invention is a compound identified using the methods of the preceding paragraph.

Another embodiment of the present invention is a method for identifying a compound or nucleic acid having the ability to reduce the activity or level of a gene product required for proliferation, said gene product comprising a gene product whose activity or expression is inhibited by an antisense nucleic acid comprising a sequence selected from the group consisting of SEQ ID NOs.: 1-93, said method comprising:

- (a) providing a target that is a gene or RNA, wherein said target comprises a nucleic acid encoding said gene product;
 - (b) contacting said target with a candidate compound or nucleic acid; and
- (c) measuring an activity of said target.

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The target may be a messenger RNA molecule and said activity may be translation of said messenger RNA. The target may be a messenger RNA molecule and said activity may be transcription of a gene encoding said messenger RNA. The target may be a gene and said activity may be transcription of said gene. The target may be a nontranslated RNA and said activity may be processing or folding of said nontranslated RNA or assembly of said nontranslated RNA into a protein/RNA complex. The target gene or RNA may encode a polypeptide comprising a sequence

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selected from the group consisting of SEQ ID NOs.: 299-305, 312-315, 327-353, 357-364, 372-458, 464-466, 468 and 472-479.

Another embodiment of the present invention is a compound or nucleic acid identified using the methods of the preceding paragraph.

Another embodiment of the present invention is a method for identifying a compound which reduces the activity or level of a gene product required for proliferation of a microorganism, wherein the activity or expression of said gene product is inhibited by an antisense nucleic acid comprising a sequence selected from the group consisting of SEQ ID NOs.: 1-93, said method comprising the steps of:

- (a) expressing a sub-lethal level of an antisense nucleic acid complementary to a nucleic acid encoding said gene product in a cell to reduce the activity or amount of said gene product in said cell, thereby producing a sensitized cell;
 - (b) contacting said sensitized cell with a compound; and

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(c) determining whether said compound inhibits the growth of said sensitized cell.

The determining step may comprise determining whether said compound inhibits the growth of said sensitized cell to a greater extent than said compound inhibits the growth of a nonsensitized cell. The cell may be selected from the group consisting of bacterial cells, fungal cells, plant cells, and animal cells. The cell may be a Gram negative bacterium. The cell may be an E. coli cell. The cell may be from an organism selected from the group consisting of Aspergillus fumigatus, Bacillus anthracis, Burkholderia cepacia, Campylobacter jejuni, Candida albicans, Candida glabrata (also called Torulopsis glabrata), Candida tropicalis, Candida parapsilosis, Candida guilliermondii, Candida krusei, Candida kefyr (also called Candida pseudotropicalis), Candida dubliniensis, Chlamydia pneumoniae, Chlamydia trachomatus, Clostridium botulinum, Clostridium difficile, Cryptococcus neoformans, Enterobacter cloacae, Enterococcus faecalis, Escherichia coli, Haemophilus influenzae, Helicobacter pylori, Klebsiella pneumoniae, Listeria monocytogenes, Mycobacterium leprae, Mycobacterium tuberculosis, Neisseria gonorrhoeae, Pseudomonas aeruginosa, Salmonella cholerasuis, Salmonella enterica, Salmonella paratyphi, Salmonella typhi, Salmonella typhimurium, Staphylococcus aureus, Klebsiella pneumoniae, Listeria monocytogenes, Moxarella catarrhalis, Shigella boydii, Shigella dysenteriae, Shigella flexneri, Shigella sonnei, Pseudomonas aeruginosa, Staphylococcus epidermidis, Streptococcus pneumoniae, Treponema pallidum, Yersinia pestis and any species falling within the genera of any of the above species. The antisense nucleic acid may be transcribed from an inducible promoter. The method may further comprise the step of contacting said cell with a concentration of inducer which induces said antisense nucleic acid to a sub-lethal level. Growth inhibition may be measured by monitoring optical density of a culture growth solution. The gene product may be a polypeptide. The polypeptide may comprise a sequence selected from the group consisting of SEQ ID NOs.: 299-

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305, 312-315, 327-353, 357-364, 372-458, 464-466, 468 and 472-479. The gene product may be an RNA.

Another embodiment of the present invention is a compound identified using the methods of the preceding paragraph.

Another embodiment of the present invention is a method for inhibiting cellular proliferation comprising introducing a compound with activity against a gene whose activity or expression is inhibited by an antisense nucleic acid comprising a sequence selected from the group consisting of SEQ ID NOs.: 1-93 or a compound with activity against the product of said gene into a population of cells expressing said gene. The compound may be an antisense nucleic acid comprising a sequence selected from the group consisting of SEQ ID NOs.: 1-93, or a proliferationinhibiting portion thereof. The proliferation inhibiting portion of one of SEQ ID NOs.: 1-93 may be a fragment comprising at least 10, at least 20, at least 30, at least 50 or more than 51 consecutive nucleotides of one of SEQ ID NOs.: 1-93. The population may be a population selected from the group consisting of bacterial cells, fungal cells, plant cells, and animal cells. The population may be a population of Gram negative bacteria. The population may be a population of E. coli cells. The population may be a population selected from the group consisting of Aspergillus fumigatus, Bacillus anthracis, Burkholderia cepacia, Campylobacter jejuni, Candida albicans, Candida glabrata (also called Torulopsis glabrata), Candida tropicalis, Candida parapsilosis, Candida guilliermondii, Candida krusei, Candida kefyr (also called Candida pseudotropicalis), Candida dubliniensis, Chlamydia pneumoniae, Chlamydia trachomatus, Clostridium botulinum, Clostridium difficile, Cryptococcus neoformans, Enterobacter cloacae, Enterococcus faecalis, Escherichia coli, Haemophilus influenzae, Helicobacter pylori, Klebsiella pneumoniae, Listeria monocytogenes, Mycobacterium leprae, Mycobacterium tuberculosis, Neisseria gonorrhoeae, Pseudomonas aeruginosa, Salmonella cholerasuis, Salmonella enterica, Salmonella paratyphi. Salmonella typhi, Salmonella typhimurium, Staphylococcus aureus, Klebsiella pneumoniae, Listeria monocytogenes, Moxarella catarrhalis, Shigella boydii, Shigella dysenteriae, Shigella flexneri. Shigella sonnei, Pseudomonas aeruginosa, Staphylococcus epidermidis, Streptococcus pneumoniae, Treponema pallidum, Yersinia pestis and any species falling within the genera of any of the above species. The gene may encode a polypeptide comprising a sequence selected from the group consisting of SEQ ID NOs.: 299-305, 312-315, 327-353, 357-364, 372-458, 464-466, 468 and 472-479.

Another embodiment of the present invention is a preparation comprising an effective concentration of an antisense nucleic acid comprising a sequence selected from the group consisting of SEQ ID NOs.: 1-93, or a proliferation-inhibiting portion thereof in a pharmaceutically acceptable carrier. The proliferation-inhibiting portion of one of SEQ ID NOs.: 1-93 may comprise at least 10, at least 20, at least 25, at least 30, at least 50 or more than 50 consecutive nucleotides of one of SEQ ID NOs.: 1-93.

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Another embodiment of the present invention is a method for inhibiting the activity or expression of a gene in an operon required for proliferation wherein the activity or expression of at least one gene in said operon is inhibited by an antisense nucleic acid comprising a sequence selected from the group consisting of SEQ ID NOs.: 1-93, said method comprising contacting a cell in a cell population with an antisense nucleic acid comprising at least a proliferation-inhibiting portion of said operon. The antisense nucleic acid comprises a sequence selected from the group consisting of SEQ ID NOs.: 1-93 or a proliferation inhibiting portion thereof.

The method of Claim 68, wherein said cell is contacted with said antisense nucleic acid by introducing a plasmid which expresses said antisense nucleic acid into said cell population. The cell may be contacted with said antisense nucleic acid by introducing a phage which expresses said antisense nucleic acid into said cell population. The cell may be contacted with said antisense nucleic acid by expressing said antisense nucleic acid from the chromosome of cells in said cell population. The cell may be contacted with said antisense nucleic acid by introducing a promoter adjacent to a chromosomal copy of said antisense nucleic acid such that said promoter directs the synthesis of said antisense nucleic acid. The cell may be contacted with said antisense nucleic acid by introducing a retron which expresses said antisense nucleic acid into said cell population. The cell may be contacted with said antisense nucleic acid by introducing a ribozyme into said cellpopulation, wherein a binding portion of said ribozyme is complementary to said antisense oligonucleotide. The cell may be contacted with said antisense nucleic acid by introducing a liposome comprising said antisense oligonucleotide into said cell. The cell may be contacted with said antisense nucleic acid by electroporation of said antisense nucleic acid. The antisense nucleic acid may be a fragment comprising at least 10, at least 20, at least 25, at least 30, at least 50 or more than 50 consecutive nucleotides of one of SEQ ID NOs.: 1-93. The antisense nucleic acid may be an oligonucleotide.

Another embodiment of the present invention is a method for identifying a gene which is required for proliferation of a microorganism comprising:

- (a) contacting a microorganism other than *E. coli* with a nucleic acid selected from the group consisting of SEQ ID NOs.: 1-93;
- (b) determining whether said nucleic acid inhibits proliferation of said microorganism;

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 - (c) identifying the gene in said microorganism which is inhibited by said nucleic acid. The microorganism may be a Gram negative bacterium. The microorganism may be selected from the group consisting of Aspergillus fumigatus, Bacillus anthracis, Burkholderia cepacia, Campylobacter jejuni, Candida albicans, Candida glabrata (also called Torulopsis glabrata), Candida tropicalis, Candida parapsilosis, Candida guilliermondii, Candida krusei, Candida kefyr (also called Candida pseudotropicalis), Candida dubliniensis, Chlamydia pneumoniae, Chlamydia trachomatus, Clostridium botulinum, Clostridium difficile, Cryptococcus neoformans,

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Enterobacter cloacae, Enterococcus faecalis, Escherichia coli, Haemophilus influenzae, Helicobacter pylori, Klebsiella pneumoniae, Listeria monocytogenes, Mycobacterium leprae, Mycobacterium tuberculosis, Neisseria gonorrhoeae, Pseudomonas aeruginosa, Salmonella cholerasuis, Salmonella enterica, Salmonella paratyphi, Salmonella typhi, Salmonella typhimurium, Staphylococcus aureus, Klebsiella pneumoniae, Listeria monocytogenes, Moxarella catarrhalis, Shigella boydii, Shigella dysenteriae, Shigella flexneri, Shigella sonnei, Pseudomonas aeruginosa, Staphylococcus epidermidis, Streptococcus pneumoniae, Treponema pallidum, Yersinia pestis and any species falling within the genera of any of the above species. The method may further comprise introducing said nucleic acid into a vector functional in said microorganism prior to introducing said inhibitory nucleic acid into said microorganism.

Another embodiment of the present invention is a method for identifying a compound having the ability to inhibit proliferation of a microorganism comprising:

- (a) identifying in a first microorganism a homolog of a gene or gene product present in a second microorganism which is different than said first microorganism, wherein the activity or level of said gene or gene product is inhibited by a nucleic acid comprising a sequence selected from the group consisting of SEQ ID NOs. 1-93;
- (b) identifying an inhibitory nucleic acid sequence which inhibits the activity of said homolog in said first microorganism;
- (c) contacting said first microorganism with a sub-lethal level of said inhibitory nucleic acid, thus sensitizing said first microorganism;
 - (d) contacting the sensitized microorganism of step (c) with a compound; and
 - (e) determining whether said compound inhibits proliferation of said sensitized microorganism.

The determining step may comprise determining whether said compound inhibits proliferation of said sensitized microorganism to a greater extent than said compound inhibits proliferation of a nonsensitized microorganism. Step (a) may comprise identifying a homologous nucleic acid to a gene or gene product whose activity or level is inhibited by a nucleic acid selected from the group consisting of SEQ ID NOs. 1-93 or a nucleic acid encoding a homologous polypeptide to a polypeptide whose activity or level is inhibited by a nucleic acid selected from the group consisting of SEQ ID NOs. 1-93 by using an algorithm selected from the group consisting of BLASTN version 2.0 with the default parameters and FASTA version 3.0t78 algorithm with the default parameters to identify said homologous nucleic acid or said nucleic acid encoding a homologous polypeptide in a database. Step (a) may comprise identifying a homologous nucleic acid or a nucleic acid encoding a homologous polypeptide by identifying nucleic acids which hybridize to said first gene. Step (a) may comprise expressing a nucleic acid selected from the group consisting of SEQ ID NOs. 1-93 in said microorganism. The inhibitory nucleic acid may be an antisense nucleic acid. The inhibitory nucleic acid may comprise an antisense nucleic acid to a portion of

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said homolog. The inhibitory nucleic acid may comprise an antisense nucleic acid to a portion of the operon encoding said homolog. The step of contacting the first microorganism with a sub-lethal level of said inhibitory nucleic acid may comprise directly contacting said microorganism with said inhibitory nucleic acid. The step of contacting the first microorganism with a sub-lethal level of said inhibitory nucleic acid may comprise expressing an antisense nucleic acid to said homolog in said microorganism. The gene product may comprise a polypeptide comprising a sequence selected from the group consisting of SEQ ID NOs.: 299-305, 312-315, 327-353, 357-364, 372-458, 464-466, 468 and 472-479.

Another embodiment of the present invention is a compound identified using the method of the preceding paragraph.

Another embodiment of the present invention is a method of identifying a compound having the ability to inhibit proliferation comprising:

- (a) contacting a microorganism other than *E. coli* with a sub-lethal level of a nucleic acid comprising a sequence selected from the group consisting of SEQ ID NOs. 1-93 or a portion thereof which inhibits the proliferation of *E. coli*, thus sensitizing said microorganism;
 - (b) contacting the sensitized microorganism of step (a) with a compound; and
- (c) determining whether said compound inhibits proliferation of said sensitized microorganism.

The determining step may comprise determining whether said compound inhibits proliferation of said sensitized microorganism to a greater extent than said compound inhibits proliferation of a nonsensitized microorganism.

Another embodiment of the present invention is a compound identified using the methods of the preceding paragraph.

Another embodiment of the present invention is a method for identifying a compound having activity against a biological pathway required for proliferation comprising:

- (a) sensitizing a cell by expressing a sub-lethal level of an antisense nucleic acid complementary to a nucleic acid encoding a gene product required for proliferation, wherein the activity or expression of said gene product is inhibited by an antisense nucleic acid comprising a sequence selected from the group consisting of SEQ ID NOs.: 1-93, in said cell to reduce the activity or amount of said gene product;
 - (b) contacting the sensitized cell with a compound; and
- (c) determining whether said compound inhibits the growth of said sensitized cell. The determining step may comprise determining whether said compound inhibits the growth of said sensitized cell to a greater extent than said compound inhibits the growth of a nonsensitized cell. The cell may be selected from the group consisting of bacterial cells, fungal cells, plant cells, and animal cells. The cell may be a Gram negative bacterium. The Gram negative bacterium may be E. coli. The cell may be selected from the group consisting of Aspergillus fumigatus, Bacillus

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anthracis, Burkholderia cepacia, Campylobacter jejuni, Candida albicans, Candida glabrata (also called Torulopsis glabrata), Candida tropicalis, Candida parapsilosis, Candida guilliermondii. Candida krusei, Candida kefyr (also called Candida pseudotropicalis), Candida dubliniensis, Chlamydia pneumoniae, Chlamydia trachomatus, Clostridium botulinum, Clostridium difficile, Cryptococcus neoformans, Enterobacter cloacae, Enterococcus faecalis, Escherichia coli, Haemophilus influenzae, Helicobacter pylori, Klebsiella pneumoniae, Listeria monocytogenes, Mycobacterium leprae, Mycobacterium tuberculosis, Neisseria gonorrhoeae, Pseudomonas aeruginosa, Salmonella cholerasuis, Salmonella enterica, Salmonella paratyphi, Salmonella typhi, Salmonella typhimurium, Staphylococcus aureus, Klebsiella pneumoniae, Listeria monocytogenes, Moxarella catarrhalis, Shigella boydii, Shigella dysenteriae, Shigella flexneri, Shigella sonnei. Pseudomonas aeruginosa, Staphylococcus epidermidis, Streptococcus pneumoniae, Treponema pallidum, Yersinia pestis and any species falling within the genera of any of the above species. The antisense nucleic acid may be transcribed from an inducible promoter. The method may further comprise contacting the cell with an agent which induces expression of said antisense nucleic acid from said inducible promoter, wherein said antisense nucleic acid is expressed at a sub-lethal level. The inhibition of proliferation may be measured by monitoring the optical density of a liquid culture. The gene product may comprise a polypeptide comprising a sequence selected from the group consisting of SEQ ID NOs.: 299-305, 312-315, 327-353, 357-364, 372-458, 464-466, 468 and 472-479.

Another embodiment of the present invention is a compound identified using the methods of the preceding paragraph.

Another embodiment of the present invention is a method for identifying a compound having the ability to inhibit cellular proliferation comprising:

- (a) contacting a cell with an agent which reduces the activity or level of a gene product required for proliferation of said cell, wherein said gene product is a gene product whose activity or expression is inhibited by an antisense nucleic acid comprising a sequence selected from the group consisting of SEQ ID NOs.: 1-93;
 - (b) contacting said cell with a compound; and
 - (c) determining whether said compound reduces proliferation of said contacted cell.

The determining step may comprise determining whether said compound reduces proliferation of said contacted cell to a greater extent than said compound reduces proliferation of cells which have not been contacted with said agent. The agent which reduces the activity or level of a gene product required for proliferation of said cell may comprise an antisense nucleic acid to a gene or operon required for proliferation. The agent which reduces the activity or level of a gene product required for proliferation of said cell may comprise a compound known to inhibit growth or proliferation of a microorganism. The cell may contain a mutation which reduces the activity or level of said gene product required for proliferation of said cell. The mutation may be a temperature sensitive

mutation. The gene product may comprise a polypeptide comprising a sequence selected from the group consisting of SEQ ID NOs.: 299-305, 312-315, 327-353, 357-364, 372-458, 464-466, 468 and 472-479.

Another embodiment of the present invention is a compound identified using the method of the preceding paragraph.

Another embodiment of the present invention is a method for identifying the biological pathway in which a proliferation-required gene or its gene product lies, wherein said gene or gene product comprises a gene or gene product whose activity or expression is inhibited by an antisense nucleic acid comprising a sequence selected from the group consisting of SEQ ID NOs.: 1-93, said method comprising:

- (a) expressing a sub-lethal level of an antisense nucleic acid which inhibits the activity of said proliferation-required gene or gene product in a cell;
- (b) contacting said cell with a compound known to inhibit growth or proliferation of a microorganism, wherein the biological pathway on which said compound acts is known; and
- (c) determining whether said cell is sensitive to said compound.

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The determining step may comprise determining whether said cell has a substantially greater sensitivity to said compound than a cell which does not express said sub-lethal level of said antisense nucleic acid and wherein said gene or gene product lies in the same pathway on which said compound acts if said cell expressing said sub-lethal level of said antisense nucleic acid has a substantially greater sensitivity to said compound than said cell which does not express said sub-lethal level of said antisense nucleic acid.

The gene product may comprise a polypeptide comprising a sequence selected from the group consisting of SEQ ID NOs.: 299-305, 312-315, 327-353, 357-364, 372-458, 464-466, 468 and 472-479.

Another embodiment of the present invention is a method for determining the biological pathway on which a test compound acts comprising:

- (a) expressing a sub-lethal level of an antisense nucleic acid complementary to a proliferation-required nucleic acid in a cell, wherein the activity or expression of said proliferation-required nucleic acid is inhibited by an antisense nucleic acid comprising a sequence selected from the group consisting of SEQ ID NOs.: 1-93 and wherein the biological pathway in which said proliferation-required nucleic acid or a protein encoded by said proliferation-required polypeptide lies is known,
 - (b) contacting said cell with said test compound; and
 - (c) determining whether said cell is sensitive to said test compound.

35 The determining step may comprise determining whether said cell has a substantially greater sensitivity to said test compound than a cell which does not express said sub-lethal level of said antisense nucleic acid. The method may further comprise:

(d) expressing a sub-lethal level of a second antisense nucleic acid complementary to a second proliferation-required nucleic acid in a second cell, wherein said second proliferation-required nucleic acid is in a different biological pathway than said proliferation-required nucleic acid in step (a); and

(e) determining whether said second cell does not have a substantially greater sensitivity to said test compound than a cell which does not express said sub-lethal level of said second antisense nucleic acid, wherein said test compound is specific for the biological pathway against which the antisense nucleic acid of step (a) acts if said second cell does not have substantially greater sensitivity to said test compound.

Another embodiment of the present invention is a purified or isolated nucleic acid comprising a sequence selected from the group consisting of SEQ ID NOs.: 1-93.

Another embodiment of the present invention is a compound which interacts with a gene or gene product whose activity or expression is inhibited by an antisense nucleic acid comprising one of SEQ ID NOs.: 1-93 to inhibit proliferation.

Another embodiment of the present invention is a compound which interacts with a polypeptide whose expression is inhibited by an antisense nucleic acid comprising one of SEQ ID NOs.: 1-93 to inhibit proliferation.

Another embodiment of the present invention is a method for manufacturing an antibiotic comprising the steps of screening one or more candidate compounds to identify a compound that reduces the activity or level of a gene product required for proliferation, said gene product comprising a gene product whose activity or expression is inhibited by an antisense nucleic acid comprising a sequence selected from the group consisting of SEQ ID NOs.: 1-93 and manufacturing the compound so identified.

The screening step may comprise performing any one of the methods of identifying a compound described above.

Another embodiment of the present invention is a method for inhibiting proliferation of a microorganism in a subject comprising administering a compound that reduces the activity or level of a gene product required for proliferation of said microorganism, said gene product comprising a gene product whose activity or expression is inhibited by an antisense nucleic acid comprising a sequence selected from the group consisting of SEQ ID NOs.: 1-93 to said subject. The method of subject may be selected from the group consisting of vertebrates, mammals, avians, and human beings. The gene product may comprise a polypeptide comprising a sequence selected from the group consisting of SEQ ID NOs.: 299-305, 312-315, 327-353, 357-364, 372-458, 464-466, 468 and 472-479.

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BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 is an IPTG dose response curve in *E. coli* transformed with an IPTG-inducible plasmid containing either an antisense clone to the *E. coli rplW* gene (AS-rplW) which encodes a ribosomal protein required for protein synthesis and essential for cell proliferation, or an antisense clone to the *elaD* gene (AS-*elaD*) which is not known to be involved in protein synthesis and which is also essential for proliferation.

Figure 2A is a tetracycline dose response curve in *E. coli* transformed with an IPTG-inducible plasmid containing antisense to the *rplW* gene (AS-*rplW*) which was carried out in the presence of 0, 20 or 50 μM IPTG.

Figure 2B is a tetracycline dose response curve in *E. coli* transformed with an IPTG-inducible plasmid containing antisense to the *elaD* gene (AS-*elaD*) which was carried out in the presence of 0, 20 or 50 μ M IPTG.

Figure 3 is a graph showing the fold increase in tetracycline sensitivity of *E. coli* transfected with antisense clones to essential ribosomal protein genes *L23* (AS-rplW) and *L7/L12* and *L10* (AS-rplLrplJ). Antisense clones to genes known not to be involved in protein synthesis (atpB/E(AS-atpB/E), visC (AS-visC), elaD (AS-elaD), yohH (AS-yohH) are much less sensitive to tetracycline.

Definitions

By "biological pathway" is meant any discrete cell function or process that is carried out by a gene product or a subset of gene products. Biological pathways include enzymatic, biochemical and metabolic pathways as well as pathways involved in the production of cellular structures such as cell walls. Biological pathways that are usually required for proliferation of microorganisms include, but are not limited to, cell division, DNA synthesis and replication, RNA synthesis (transcription), protein synthesis (translation), protein processing, protein transport, fatty acid biosynthesis, cell wall synthesis, cell membrane production, synthesis and maintenance, and the like.

By "inhibit activity of a gene or gene product" is meant having the ability to interfere with the function of a gene or gene product in such a way as to decrease expression of the gene or to reduce the level or activity of a product of the gene. Agents which inhibit the activity of a gene include agents that inhibit transcription of the gene, agents that inhibit processing of the transcript of the gene, agents that reduce the stability of the transcript of the gene, and agents that inhibit translation of the mRNA transcribed from the gene. In microorganisms, agents which inhibit the activity of a gene can act to decrease expression of the operon in which the gene resides or alter the folding or processing of operon RNA so as to reduce the level or activity of the gene product. The gene product can be a non-translated RNA such as ribosomal RNA, a translated RNA (mRNA) or

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the protein product resulting from translation of the gene mRNA. Of particular utility to the present invention are antisense RNAs that have activities against the operons or genes to which they specifically hybridze.

By "activity against a gene product" is meant having the ability to inhibit the function or to reduce the level or activity of the gene product in a cell.

By "activity against a protein" is meant having the ability to inhibit the function or to reduce the level or activity of the protein in a cell.

By "activity against a nucleic acid" is meant having the ability to inhibit the function or to reduce the level or activity of the nucleic acid in a cell.

By "activity against a gene" is meant having the ability to inhibit the function or expression of the gene in a cell.

By "activity against an operon" is meant having the ability to inhibit the function or reduce the level of one or more products of the operon in a cell.

By "antibiotic" is meant an agent which inhibits the proliferation of a microorganism.

By "E. coli or Escherichia coli" is meant Escherichia coli or any organism previously categorized as a species of Shigella including Shigella boydii, Shigella flexneri, Shigella dysenteriae, Shigella sonnei, Shigella 2A.

By "identifying a compound" is meant to screen one or more compounds in a collection of compounds such as a combinatorial chemical library or other library of chemical compounds or to characterize a single compound by testing the compound in a given assay and determining whether it exhibits the desired activity.

By "inducer" is meant an agent or solution which, when placed in contact with a microorganism, increases transcription from a desired promoter.

As used herein, "nucleic acid" means DNA, RNA, or modified nucleic acids. Thus, the terminology "the nucleic acid of SEQ ID NO: X" includes both the DNA sequence of SEQ ID NO: X and an RNA sequence in which the thymidines in the DNA sequence have been substituted with uridines in the RNA sequence and in which the deoxyribose backbone of the DNA sequence has been substituted with a ribose backbone in the RNA sequence. Modified nucleic acids are nucleic acids having nucleotides or structures which do not occur in nature, such as nucleic acids in which internucleotide phosphate residues with methylphosphonates, phosphorothioates, phosphoramidates, and phosphate esters. Nonphosphate internucleotide analogs such as siloxane bridges, carbonate brides, thioester bridges, as well as many others known in the art may also be used in modified nucleic acids. Modified nucleic acids may also comprise, a-anomeric nucleotide modified nucleotides units and such as 1,2-dideoxy-d-ribofuranose, 1,2-dideoxy-1phenylribofuranose, and N^4 , N^4 -ethano-5-methyl-cytosine are contemplated for use in the present Modified nucleic acids may also be peptide nucleic acids in which the entire invention.

deoxyribose-phosphate backbone has been exchanged with a chemically completely different, but structurally homologous, polyamide (peptide) backbone containing 2-aminoethyl glycine units.

As used herein, "sub-lethal" means a concentration of an agent below the concentration required to inhibit all cell growth.

DETAILED DESCRIPTION OF THE INVENTION

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The present invention describes a group of E. coli genes and gene families required for growth and/or proliferation. A proliferation-required gene or gene family is one where, in the absence of a gene transcript and/or gene product, growth or viability of the microorganism is reduced or eliminated. Thus, as used herein the terminology "proliferation-required" or "required for proliferation" encompasses instances where the absence of a gene transcript and/or gene product completely eliminates cell growth as well as instances where the absence of a gene transcript and/or gene product merely reduces cell growth. These proliferation-required genes can be used as potential targets for the generation of new antimicrobial agents. To achieve that goal, the present invention also encompasses novel assays for analyzing proliferation-required genes and for identifying compounds which interact with the gene products of the proliferation-required genes. In addition, the present invention contemplates the expression of genes and the purification of the proteins encoded by the nucleic acid sequences identified as required proliferation genes and reported herein. The purified proteins can be used to generate reagents and screen small molecule libraries or other candidate compound libraries for compounds that can be further developed to yield novel antimicrobial compounds. The present: invention also describes methods for identification of homologous genes or polypeptides in organisms other than E. coli.

The present invention utilizes a novel method to identify proliferation-required *E. coli* sequences. Generally, a library of nucleic acid sequences from a given source are subcloned or otherwise inserted into an inducible expression vector, thus forming an expression library. Although the insert nucleic acids may be derived from the chromosome of the organism into which the expression vector is to be introduced, because the insert is not in its natural chromosomal location, the insert nucleic acid is an exogenous nucleic acid for the purposes of the discussion herein. The term expression is defined as the production of an RNA molecule from a gene, gene fragment, genomic fragment, or operon. Expression can also be used to refer to the process of peptide or polypeptide synthesis. An expression vector is defined as a vehicle by which a ribonucleic acid (RNA) sequence is transcribed from a nucleic acid sequence carried within the expression vehicle. The expression vector can also contain features that permit translation of a protein product from the transcribed RNA message expressed from the exogenous nucleic acid sequence carried by the expression vector. Accordingly, an expression vector can produce an RNA molecule as its sole product or the expression vector can produce a RNA molecule that is ultimately translated into a protein product.

Once generated, the expression library containing the exogenous nucleic acid sequences is introduced into an *E. coli* population to search for genes that are required for bacterial proliferation.

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Because the library molecules are foreign to the population of *E. coli*, the expression vectors and the nucleic acid segments contained therein are considered exogenous nucleic acid.

Expression of the exogenous nucleic acid fragments in the test population of *E. coli* containing the expression vector library is then activated. Activation of the expression vectors consists of subjecting the cells containing the vectors to conditions that result in the expression of the exogenous nucleic acid sequences carried by the expression vector library. The test population of *E. coli* cells is then assayed to determine the effect of expressing the exogenous nucleic acid fragments on the test population of cells. Those expression vectors that, upon activation and expression, negatively impact the growth of the *E. coli* screen population are identified, isolated, and purified for further study.

A variety of assays are contemplated to identify nucleic acid sequences that negatively impact growth upon expression. In one embodiment, growth in *E. coli* cultures expressing exogenous nucleic acid sequences is compared to growth in cultures not expressing these sequences. Optical density is used to monitor the extent of growth. Alternatively, enzymatic assays can be used to determine bacterial growth rates to identify exogenous nucleic acid sequences of interest. Colony size, colony morphology, and cell morphology are additional factors used to evaluate growth of the host cells. Those cultures that fail to grow or grow at a reduced rate under expression conditions are identified as containing an expression vector encoding a nucleic acid fragment that negatively affects a proliferation-required gene.

Once exogenous nucleic acid sequences of interest are identified, they are analyzed. The first step of the analysis is to acquire the nucleic acid sequence of the nucleic acid fragment of interest. To achieve this end, the insert in those expression vectors identified as containing a sequence of interest is sequenced, using standard techniques well known in the art. The next step of the process is to determine the source of the nucleic acid sequence.

Determination of sequence source is achieved by comparing the obtained sequence data with known sequences in various genetic databases. The sequences identified are used to probe these gene databases. The result of this procedure is a list of exogenous nucleic acid sequences corresponding to a list that includes novel bacterial genes required for proliferation as well as genes previously identified as required for proliferation.

The number of DNA and protein sequences available in database systems has been growing exponentially for years. For example, at the end of 1998, the complete sequences of *Caenorhabditis elegans*, *Saccharomyces cerevisiae* and nineteen bacterial genomes, including *E. coli* were available. This sequence information is stored in a number of databanks, such as GenBank (the National Center for Biotechnology Information (NCBI), and is publicly available for searching.

A variety of computer programs are available to assist in the analysis of the sequences stored within these databases. FASTA, (W. R. Pearson (1990) "Rapid and Sensitive Sequence Comparison with FASTP and FASTA" Methods in Enzymology 183:63-98), Sequence Retrieval System (SRS), (Etzold & Argos, SRS an indexing and retrieval tool for flat file data libraries. Comput. Appl.

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Biosci. 9:49-57, 1993) are two examples of computer programs that can be used to analyze sequences of interest. In one embodiment of the present invention, the BLAST family of computer programs, which includes BLASTN version 2.0 with the default parameters, or BLASTX version 2.0 with the default parameters, is used to analyze nucleic acid sequences. BLAST, an acronym for "Basic Local Alignment Search Tool," is a family of programs for database similarity searching. The BLAST family of programs includes: BLASTN, a nucleotide sequence database searching program, BLASTX, a protein database searching program where the input is a nucleic acid sequence; and BLASTP, a protein database searching program where the input is an amino acid sequence. BLAST programs embody a fast algorithm for sequence matching, rigorous statistical methods for judging the significance of matches, and various options for tailoring the program for special situations. Assistance in using the program can be obtained by e-mail at blast@ncbi.nlm.nih.gov.

Bacterial genes are often transcribed in polycistronic groups. These groups comprise operons, which are a collection of genes and intergenic sequences. The genes of an operon are co-transcribed and often have related functions. Given the nature of the screening protocol, it is possible that the identified exogenous nucleic acid sequence corresponds to a gene or portion thereof with or without adjacent noncoding sequences, an intragenic sequence (i.e. a sequence within a gene), an intergenic sequence (i.e. a sequence between genes), a sequence spanning at least a portion of two or more genes, a 5' noncoding region or a 3' noncoding region located upstream or downstream from the actual sequence that is required for bacterial proliferation. Accordingly, determining which gene(s) that is encoded within the operons is individually required for proliferation is often desirable.

In one embodiment of the present invention, an operon is dissected to determine which gene or genes are required for proliferation. For example, the RegulonDB DataBase described by Huerta et al. (Nucl. Acids Res. 26:55-59, 1998), which may also be found on the website http://www.cifn.unam.mx/Computational_Biology/regulondb/,may be used to identify the boundaries of operons encoded within microbial genomes. A number of techniques that are well known in the art can then be used to dissect the operon. In one aspect of this embodiment, gene disruption by homologous recombination is used to individually inactivate the genes of an operon that is thought to contain a gene required for proliferation.

Several gene disruption techniques have been described for the replacement of a functional gene with a mutated, non-functional (null) allele. These techniques generally involve the use of homologous recombination. The method described by Link et al. (J. Bacteriol 1997 179:6228) serves as an excellent example of these methods as applicable to disruption of genes in *E. coli*. This technique uses crossover PCR to create a null allele with an in-frame deletion of the coding region of a target gene. The null allele is constructed in such a way that sequences adjacent to the wild type gene (ca. 500 bp) are retained. These homologous sequences surrounding the deletion null-

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allele provide targets for homologous recombination so that the wild type gene on the *E. coli* chromosome can be replaced by the constructed null allele.

The crossover PCR amplification product is subcloned into the vector pKO3, the features of which include a chloramphenical resistance gene, the counter-selectable marker sacB, and a temperature sensitive autonomous replication function. Following transformation of an E. coli cell population with such a vector, selection for cells that have undergone homologous recombination of the vector into the chromosome is achieved by growth on chloramphenical at the non-permissive temperature of 43°C. Under these conditions, autonomous replication of the plasmid cannot occur and cells are resistant to chloramphinical only if the chloramphenical resistance gene has been integrated into the chromosome. Usually a single crossover event is responsible for this integration event such that the E. coli chromosome now contains a tandem duplication of the target gene consisting of one wild type allele and one deletion null allele separated by vector sequence.

This new *E. coli* strain containing the tandem duplication can be maintained at permissive temperatures in the presence of drug selection (chloramphenicol). Subsequently, cells of this new strain are cultured at the permissive temperature 30°C without drug selection. Under these conditions, the chromosome of some of the cells within the population will have undergone an internal homologous recombination event resulting in removal of the plasmid sequences. Subsequent culturing of the strain in growth medium lacking chloramphenicol but containing sucrose is used to select for such recombinative resolutions. In the presence of the counter-selectable marker *sacB*, sucrose is rendered into a toxic metabolite. Thus, cells that survive this counter-selection have lost both the plasmid sequences from the chromosome and the autonomously replicating plasmid that results as a byproduct of recombinative resolution.

There are two possible outcomes of the above recombinative resolution via homologous recombination. Either the wild type copy of the targeted gene is retained on the chromosome or the mutated null allele is retained on the chromosome. In the case of an essential gene, a single copy of the null allele would be lethal and such cells should not be obtained by the above procedure when applied to essential genes. In the case of a non-essential gene, roughly equal numbers of cells containing null alleles and cells containing wild type alleles should be obtained. Thus, the method serves as a test for essentiality of the targeted gene: when applied to essential genes, only cells with a wild type allele on the chromosome will be obtained.

Other techniques have also been described for the creation of disruption mutations in *E. coli*. For example, Link et al. also describe inserting an in-frame sequence tag concommitantly with an in-frame deletion in order to simplify analysis of recombinants obtained. Further, Link et al. describe disruption of genes with a drug resistance marker such as a kanamycin resistance gene. Arigoni et al., (Arigoni, F. et al. A Genome-based Approach for the Identification of Essential Bacterial Genes, Nature Biotechnology 16: 851-856) describe the use of gene disruption combined with engineering a second copy of a test gene such that the expression of the gene is regulated by

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and inducible promoter such as the arabinose promoter to test the essentiality of the gene. Many of these techniques result in the insertion of large fragments of DNA into the gene of interest, such as a drug selection marker. An advantage of the technique described by Link et al. is that it does not rely on an insertion into the gene to cause a functional defect, but rather results in the precise removal of the coding region. This insures the lack of polar effects on the expression of genes downstream from the target gene.

Recombinant DNA techniques can be used to express the entire coding sequences of the gene identified as required for proliferation, or portions thereof. The over-expressed proteins can be used as reagents for further study. The identified exogenous sequences are isolated, purified, and cloned into a suitable expression vector using methods well known in the art. If desired, the nucleic acids can contain the sequences encoding a signal peptide to facilitate secretion of the expressed protein.

Expression of fragments of the bacterial genes identified as required for proliferation is also contemplated by the present invention. The fragments of the identified genes can encode a polypeptide comprising at least 5, at least 10, at least 15, at least 20, at least 25, at least 30, at least 35, at least 40, at least 45, at least 50, at least 55, at least 60, at least 65, at least 75, or more than 75 consecutive amino acids of a gene complementary to one of the identified sequences of the present invention. The nucleic acids inserted into the expression vectors can also contain sequences upstream and downstream of the coding sequence.

When expressing the coding sequence of an entire gene identified as required for bacterial proliferation or a fragment thereof, the nucleic acid sequence to be expressed is operably linked to a promoter in an expression vector using conventional cloning technology. The expression vector can be any of the bacterial, insect, yeast, or mammalian expression systems known in the art. Commercially available vectors and expression systems are available from a variety of suppliers including Genetics Institute (Cambridge, MA), Stratagene (La Jolla, California), Promega (Madison, Wisconsin), and Invitrogen (San Diego, California). If desired, to enhance expression and facilitate proper protein folding, the codon usage and codon bias of the sequence can be optimized for the particular expression organism in which the expression vector is introduced, as explained by Hatfield, et al., U.S. Patent No. 5,082,767. Fusion protein expression systems are also contemplated by the present invention.

Following expression of the protein encoded by the identified exogenous nucleic acid sequence, the protein is purified. Protein purification techniques are well known in the art. Proteins encoded and expressed from identified exogenous nucleic acid sequences can be partially purified using precipitation techniques, such as precipitation with polyethylene glycol. Alternatively, epitope tagging of the protein can be used to allow simple one step purification of the protein. Chromatographic methods usable with the present invention can include ion-exchange chromatography, gel filtration, use of hydroxyapaptite columns, immobilized reactive dyes, chromatofocusing, and use of high-performance liquid chromatography. Electrophoretic methods such one-dimensional gel electrophoresis, high-resolution two-dimensional polyacrylamide electrophoresis,

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isoelectric focusing, and others are contemplated as purification methods. Also, affinity chromatographic methods, comprising antibody columns, ligand presenting columns and other affinity chromatographic matrices are contemplated as purification methods in the present invention.

The purified proteins produced from the gene coding sequences identified as required for proliferation can be used in a variety of protocols to generate useful antimicrobial reagents. In one embodiment of the present invention, antibodies are generated against the proteins expressed from the identified exogenous nucleic acid sequences. Both monoclonal and polyclonal antibodies can be generated against the expressed proteins. Methods for generating monoclonal and polyclonal antibodies are well known in the art. Also, antibody fragment preparations prepared from the produced antibodies discussed above are contemplated.

In addition, the purified protein, fragments therof, or derivatives thereof may be administered to an individual in a pharmaceutically acceptable carrier to induce an immune response against the protein. Preferably, the immune response is a protective immune response which protects the individual. Methods for determining appropriate dosages of the protein and pharmaceutically acceptable carriers are familiar to those skilled in the art.

Another application for the purified proteins of the present invention is to screen small molecule libraries for candidate compounds active against the various target proteins of the present invention. Advances in the field of combinatorial chemistry provide methods, well known in the art, to produce large numbers of candidate compounds that can have a binding, or otherwise inhibitory effect on a target protein. Accordingly, the screening of small molecule libraries for compounds with binding affinity or inhibitory activity for a target protein produced from an identified gene sequence is contemplated by the present invention.

The present invention further contemplates utility against a variety of other pathogenic organisms in addition to E. coli. For example, the invention has utility in identifying genes required for proliferation in prokaryotes and eukaryotes. For example, the invention has utility with protists, such as Plasmodium spp. and as Entamoeba spp., plants; animals, such and Contracaecum spp., and fungi including Candida spp., ((e.g., Candida albicansCandida glabrata (also called Torulopsis glabrata), Candida tropicalis, Candida parapsilosis, Candida guilliermondii, Candida krusei, Candida kefyr (also called Candida pseudotropicalis), Candida dubliniensis,)), Saccharomyces cerevisiae, Cryptococcus neoformans, and Aspergillus fumigatus. In one embodiment of the present invention, monera, specifically bacteria are probed in search of novel gene sequences required for proliferation. This embodiment is particularly important given the rise of drug resistant bacteria.

The numbers of bacterial species that are becoming resistant to existing antibiotics are growing. A partial list of these organisms includes: Staphylococcus spp., such as S. aureus; Enterococcus spp., such as E. faecalis; Pseudomonas spp., such as P. aeruginosa, Clostridium spp., such as C. botulinum or C. difficile, Haemophilus spp., such as H. influenzae, Enterobacter spp., such as E. cloacae, Vibrio spp., such as V. cholera; Moraxala spp., such as M. catarrhalis;

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Streptococcus spp., such as S. pneumoniae, Neisseria spp., such as N. gonorrhoeae; Mycoplasma spp., such as Mycoplasma pneumoniae; Salmonella typhimurium; Helicobacter pylori; Escherichia coli; and Mycobacterium tuberculosis. The sequences identified as required for proliferation in the present invention can be used to probe these and other organisms to identify homologous required proliferation genes contained therein.

In one embodiment of the present invention, the nucleic acid sequences disclosed herein are used to screen genomic libraries generated from bacterial species of interest other than E. coli. For example, the genomic library may be from Aspergillus fumigatus, Bacillus anthracis, Burkholderia cepacia, Campylobacter jejuni, Candida albicans, Candida glabrata (also called Torulopsis glabrata), Candida tropicalis, Candida parapsilosis, Candida guilliermondii, Candida krusei, Candida kefyr (also called Candida pseudotropicalis), Candida dubliniensis, Chlamydia pneumoniae, Chlamydia trachomatus, Clostridium botulinum, Cryptococcus neoformans, Enterobacter cloacae, Enterococcus faecalis, Haemophilus influenzae, Helicobacter pylori, Klebsiella pneumoniae, Listeria monocytogenes, Mycobacterium leprae, Mycobacterium tuberculosis, Neisseria gonorrhoeae, Pseudomonas aeruginosa, Salmonella cholerasuis, Salmonella enterica, Salmonella paratyphi, Salmonella typhi, Salmonella typhimurium, Staphylococcus aureus, Klebsiella pneumoniae, Listeria monocytogenes, Moxarella catarrhalis, Shigella boydii, Shigella dysenteriae, Shigella flexneri, Shigella sonnei, Pseudomonas aeruginosa, Staphylococcus epidermidis, Streptococcus pneumoniae, Treponema pallidum, Yersinia pestis or any species falling within the genera of any of the above species. Standard molecular biology techniques are used to generate genomic libraries from various microorganisms. In one aspect, the libraries are generated and bound to nitrocellulose paper. The identified exogenous nucleic acid sequences of the present invention can then be used as probes to screen the libraries for homologous sequences. The homologous sequences identified can then be used as targets for the identification of new, antimicrobial compounds with activity against more than one organism.

For example, the preceding methods may be used to isolate nucleic acids having a sequence with at least 97%, at least 95%, at least 80%, or at least 70% identity to a nucleic acid sequence selected from the group consisting of one of the sequences of SEQ ID NOS. 1-93, 106-112, 119-122, 134-160, 164-171, 179-265, 271-273, 275, and 279-286, fragments comprising at least 10, 15, 20, 25, 30, 35, 40, 50, 75, 100, 150, 200, 300, 400, or 500 consecutive nucleotides thereof, and the sequences complementary thereto. Identity may be measured using BLASTN version 2.0 with the default parameters. (Altschul, S.F. et al. Gapped BLAST and PSI-BLAST: A New Generation of Protein Database Search Programs, Nucleic Acid Res. 25: 3389-3402 (1997)). For example, the homologous polynucleotides may have a coding sequence which is a naturally occurring allelic variant of one of the coding sequences described herein. Such allelic variants may have a substitution, deletion or addition of one or more nucleotides when compared to

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the nucleic acids of SEQ ID NOs: 1-93, 106-112, 119-122, 134-160, 164-171, 179-265, 271-273, 275, and 279-286 or the sequences complementary thereto.

Additionally, the above procedures may be used to isolate nucleic acids which encode polypeptides having at least 99%, 95%, at least 90%, at least 85%, at least 80%, at least 70%, at least 60%, at least 50%, or at least 40% identity or similarity to a polypeptide having the sequence of one of SEQ ID NOs: 299-305, 312-315, 327-353, 357-364, 372-458, 464-466, 468 and 472-479 or to a polypeptide whose expression is inhibited by a nucleic acid of one of SEQ ID NOs.: 1-93, or fragments comprising at least 5, 10, 15, 20, 25, 30, 35, 40, 50, 75, 100, or 150 consecutive amino acids of the preceding polypeptides as determined using the FASTA version 3.0t78 algorithm with the default parameters. Alternatively, protein identity or similarity may be identified using BLASTP with the default parameters, BLASTX with the default parameters, or TBLASTN with the default parameters. (Alschul, S.F. et al. Gapped BLAST and PSI-BLAST: A New Generation of Protein Database Search Programs, Nucleic Acid Res. 25: 3389-3402 (1997)).

Alternatively, homologous nucleic acids or polypeptides may be identified by searching a database to identify sequences having a desired level of homology to a nucleic acid or a polypeptide involved in proliferation or an antisense nucleic acid to a nucleic acid involved in microbial proliferation. A variety of such databases are available to those skilled in the art, including GenBank and GenSeq. In some embodiments, the databases are screened to identify nucleic acids or polypeptides having at least 97%, at least 95%, at least 90%, at least 85%, at least 80%, at least 70%, at least 60%, or at least 50%, at least 40% identity or similarity to a nucleic acid or polypeptide involved in proliferation or an antisense nucleic acid involved in proliferation. For example, the database may be screened to identify nucleic acids homologous to one of SEQ ID Nos. 1-93, 106-112, 119-122, 134-160, 164-171, 179-265, 271-273, 275, and 279-286, homologous to fragments comprising at least 10, 15, 20, 25, 30, 35, 40, 50, 75, 100, 150, 200, 300, 400, or 500 consecutive nucleotides thereof, or homologous to the sequences complementary to any of the preceding nucleic acids. In other embodiments, the databases are screened to indetify polypeptides having at least 99%, 95%, 90%, 855, 80%, 70%, 60%, 50%, 40%, or at least 25% identity or similarity of a polypeptide involved in proliferation or a portion thereof. For example, the database may be screened to identify polypeptides homologous to a polypeptide comprising one of SEQ ID NOs. 299-305, 312-315, 327-353, 357-364, 372-458, 464-466, 468 and 472-479, a polypeptide whose expression is inhibited by a nucleic acid of one of SEQ ID NOs: 1-93, or homologous to fragments comprising at least 5, 10, 15, 20, 25, 30, 35, 40, 50, 75, 100, or 150 consecutive amino acids of any of the preceding polypeptides. In some embodiments, the database may be screened to identify homologous nucleic acids or polypeptides from organisms other than E. coli, including organisms such as Aspergillus fumigatus, Bacillus anthracis, Burkholderia cepacia, Campylobacter jejuni, Candida albicans, Candida glabrata (also called Torulopsis glabrata), Candida tropicalis, Candida parapsilosis, Candida guilliermondii, Candida krusei, Candida kefyr

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(also called Candida pseudotropicalis), Candida dubliniensis, Candida glabrata (also called Torulopsis glabrata), Candida tropicalis, Candida parapsilosis, Candida guilliermondii, Candida krusei, Candida kefyr (also called Candida pseudotropicalis), Candida dubliniensis, Candida glabrata (also called Torulopsis glabrata), Candida tropicalis, Candida parapsilosis, Candida guilliermondii, Candida krusei, Candida kefyr (also called Candida pseudotropicalis), Candida dubliniensis, Chlamydia pneumoniae, Chlamydia trachomatus, Clostridium botulimum, Clostridium difficile, Cryptococcus neoformans, Enterobacter cloacae, Enterococcus faecalis, Haemophilus influenzae, Helicobacter pylori, Klebsiella pneumoniae, Listeria monocytogenes, Mycobacterium leprae, Mycobacterium tuberculosis, Neisseria gonorrhoeae, Pseudomonas aeruginosa, Salmonella cholerasuis, Salmonella enterica, Salmonella paratyphi, Salmonella typhi, Salmonella typhimurium, Staphylococcus aureus, Klebsiella pneumoniae, Listeria monocytogenes, Moxarella catarrhalis, Shigella boydii, Shigella dysenteriae, Shigella flexneri, Shigella sonnei, Pseudomonas aeruginosa, Staphylococcus epidermidis, Streptococcus pneumoniae, Treponema pallidum, Yersinia pestis or any species falling within the genera of any of the above species.

In another embodiment, gene expression arrays and microarrays can be employed. Gene expression arrays are high density arrays of DNA samples deposited at specific locations on a glass chip, nylon membrane, or the like. Such arrays can be used by researchers to quantify relative gene expression under different conditions. Gene expression arrays are used by researchers to help identify optimal drug targets, profile new compounds, and determine disease pathways. An example of this technology is found in U.S. Patent No. 5807522.

It is possible to study the expression of all genes in the genome of a particular microbial organism using a single array. For example, the arrays from Genosys consist of 12 x 24 cm nylon filters containing PCR products corresponding to 4290 ORFs from E. coli. 10 ngs of each are spotted every 1.5 mm on the filter. Single stranded labeled cDNAs are prepared for hybridization to the array (no second strand synthesis or amplification step is done) and placed in contact with the filter. Thus the labeled cDNAs are of "antisense" orientation. Quantitative analysis is done by phosphorimager.

Hybridization of cDNA made from a sample of total cell mRNA to such an array followed by detection of binding by one or more of various techniques known to those in the art results in a signal at each location on the array to which cDNA hybridized. The intensity of the hybridization signal obtained at each location in the array thus reflects the amount of mRNA for that specific gene that was present in the sample. Comparing the results obtained for mRNA isolated from cells grown under different conditions thus allows for a comparison of the relative amount of expression of each individual gene during growth under the different conditions.

Gene expression arrays may be used to analyze the total mRNA expression pattern at various time points after induction of an antisense nucleic acid complementary to a proliferation-required gene. Analysis of the expression pattern indicated by hybridization to the array provides

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information on whether or not the target gene of the antisense nucleic acid is being affected by antisense induction, how quickly the antisense is affecting the target gene, and for later timepoints, what other genes are affected by antisense expression. For example, if the antisense is directed against a gene for ribosomal protein L7/L12 in the 50S subunit, its targeted mRNA may disappear first and then other mRNAs may be observed to increase, decrease or stay the same. Similarly, if the antisense is directed against a different 50S subunit ribosomal protein mRNA (e.g. L25), that mRNA may disappear first followed by changes in mRNA expression that are similar to those seen with the L7/L12 antisense expression. Thus, the mRNA expression pattern observed with an antinsense nucleic acid complementary to a proliferation required gene may identify other proliferation-required nucleic acids in the same pathway as the target of the antisense nucleic acid. In addition, the mRNA expression patterns observed with candidate drug compounds may be compared to those observed with antisense nucleic acids against a proliferation-required nucleic acid. If the mRNA expression pattern observed with the candidate drug compound is similar to that observed with the antisense nucleic acid, the drug compound may be a promising therapeutic candidate. Thus, the assay would be useful in assisting in the selection of candidate drug compounds for use in screening methods such as those described below.

In cases where the source of nucleic acid deposited on the array and the source of the nucleic acid being hybridized to the array are from two different organisms, gene expression arrays can identify homologous genes in the two organisms.

The present invention also contemplates additional methods for screening other microorganisms for proliferation-required genes. In this embodiment, the conserved portions of sequences identified as proliferation-required can be used to generate degenerate primers for use in the polymerase chain reaction (PCR). The PCR technique is well known in the art. The successful production of a PCR product using degenerate probes generated from the sequences identified herein would indicate the presence of a homologous gene sequence in the species being screened. This homologous gene is then isolated, expressed, and used as a target for candidate antibiotic compounds. In another aspect of this embodiment, the homologous gene is expressed in an autologous organism or in a heterologous organism in such a way as to alter the level or activity of a homologous gene required for proliferation in the autologous or heterologus organism. In still another aspect of this embodiment, the homologous gene or portion is expressed in an antisense orientation in such a way as to alter the level or activity of a nucleic acid required for proliferation of an autologous or heterologous organism.

The homologous sequences to proliferation-required genes identified using the techniques described herein may be used to identify proliferation-required genes of organisms other than *E. coli*, to inhibit the proliferation of organisms other than *E. coli* by inhibiting the activity or reducing the amount of the identified homologous nucleic acid or polypeptide in the organism other than *E. coli*, or to identify compounds which inhibit the growth of organisms other than *E. coli* as described below.

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In another embodiment of the present invention, *E. coli* sequences identified as required for proliferation are transferred to expression vectors capable of function within non-*E coli* species. As would be appreciated by one of ordinary skill in the art, expression vectors must contain certain elements that are species specific. These elements can include promoter sequences, operator sequences, repressor genes, origins of replication, selectable marker genes, ribosomal binding sequences, termination sequences, and others. To use the identified exogenous sequences of the present invention, one of ordinary skill in the art would know to use standard molecular biology techniques to isolate vectors containing the sequences of interest from cultured bacterial cells, isolate and purify those sequences, and subclone those sequences into an expression vector adapted for use in the species of bacteria to be screened.

Expression vectors for a variety of other species are known in the art. For example, Cao et al. report the expression of steroid receptor fragments in *Staphylococcus aureus*. J. Steroid Biochem Mol Biol. 44(1):1-11 (1993). Also, Pla et al. have reported an expression vector that is functional in a number of relevant hosts including: *Salmonella typhimurium*, *Pseudomonas putido*, and *Pseudomonas aeruginosa*. J. Bacteriol. 172(8):4448-55 (1990). These examples demonstrate the existence of molecular biology techniques capable of constructing expression vectors for the species of bacteria of interest to the present invention.

Following the subcloning of the identified nucleic acid sequences into an expression vector functional in the microorganism of interest, the identified nucleic acid sequences are conditionally transcribed to assay for bacterial growth inhibition. Those expression vectors found to contain sequences that, when transcribed, inhibit bacterial growth are compared to the known genomic sequence of the pathogenic microorganism being screened or, if the homologous sequence from the organism being screened is not known, it may be identified and isolated by hybridization to the proliferation-required *E. coli* sequence interest or by amplification using primers based on the proliferation-required *E. coli* sequence of interest as described above.

The antisense sequences from the second organism which are identified as described above may then be operably linked to a promoter, such as an inducible promoter, and introduced into the second organism. The techniques described herein for identifying *E. coli* genes required for proliferation may thus be employed to determine whether the identified sequences from a second organism inhibit the proliferation of the second organism.

Antisense nucleic acids required for the proliferation of organisms other than *E. coli* or the genes corresponding thereto, may also be hybridized to a microarray containing the *E. coli* ORFs to gauge the homology between the *E. coli* sequences and the proliferation-required nucleic acids from other organisms. For example, the proliferation-required nucleic acid may be from *Aspergillus fumigatus*, *Bacillus anthracis*, *Burkholderia cepacia*, *Campylobacter jejuni*, *Candida albicans*, *Candida glabrata (also called Torulopsis glabrata)*, *Candida tropicalis*, *Candida parapsilosis*, *Candida guilliermondii*, *Candida krusei*, *Candida kefyr* (also called Candida pseudotropicalis),

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Candida dubliniensis, Chlamydia pneumoniae, Chlamydia trachomatus, Clostridium botulinum, Clostridium difficile, Cryptococcus neoformans, Enterobacter cloacae, Enterococcus faecalis, Haemophilus influenzae, Helicobacter pylori, Klebsiella pneumoniae, Listeria monocytogenes, Mycobacterium leprae, Mycobacterium tuberculosis, Neisseria gonorrhoeae, Pseudomonas aeruginosa, Salmonella cholerasuis, Salmonella enterica, Salmonella paratyphi, Salmonella typhi, Salmonella typhimurium, Staphylococcus aureus, Klebsiella pneumoniae, Listeria monocytogenes, Moxarella catarrhalis, Shigella boydii, Shigella dysenteriae, Shigella flexneri, Shigella sonnei, Pseudomonas aeruginosa, Staphylococcus epidermidis, Streptococcus pneumoniae, Treponema pallidum, Yersinia pestis or any species falling within the genera of any of the above species. The proliferation-required nucleic acids from an organism other than E. coli may be hybridized to the array under a variety of conditions which permit hybridization to occur when the probe has different levels of homology to the sequence on the microarray. This would provide an indication of homology across the organisms as well as clues to other possible essential genes in these organisms.

In still another embodiment, the exogenous nucleic acid sequences of the present invention that inhibit bacterial growth or proliferation can be used as antisense therapeutics for killing bacteria. The antisense sequences can be complementary to the proliferation-required genes whose sequence corresponds to the exogenous nucleic acid probes identified here (i.e. the antisense nucleic acid may hybridize to the gene or a portion thereof). Alternatively, antisense therapeutics can be complementary to operons in which proliferation-required genes reside (i.e. the antisense nucleic acid may hybridize to any gene in the operon in which the proliferation-required genes reside). Further, antisense therapeutics can be complementary to a proliferation-required gene or portion thereof with or without adjacent noncoding sequences, an intragenic sequence (i.e. a sequence within a gene), an intergenic sequence (i.e. a sequence between genes), a sequence spanning at least a portion of two or more genes, a 5' noncoding region or a 3' noncoding region located upstream or downstream from the actual sequence that is required for bacterial proliferation or an operon containing a proliferation-required gene.

In addition to therapeutic applications, the present invention encompasses the use of nucleic acid sequences complementary to sequences required for proliferation as diagnostic tools. For example, nucleic acid probes complementary to proliferation-required sequences that are specific for particular species of microorganisms can be used as probes to identify particular microorganism species in clinical specimens. This utility provides a rapid and dependable method by which to identify the causative agent or agents of a bacterial infection. This utility would provide clinicians the ability to prescribe species specific antimicrobial compounds to treat such infections. In an extension of this utility, antibodies generated against proteins translated from mRNA transcribed from proliferation-required sequences can also be used to screen for specific microorganisms that produce such proteins in a species-specific manner.

The following examples teach the genes of the present invention and a subset of uses for the *E. coli* genes identified as required for proliferation. These examples are illustrative only and are not intended to limit the scope of the present invention.

EXAMPLES

The following examples are directed to the identification and exploitation of *E. coli* genes required for proliferation. Methods of gene identification are discussed as well as a variety of methods to utilize the identified sequences.

Genes Identified as Required for Proliferation of E. coli

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Exogenous nucleic acid sequences were cloned into an inducible expression vector and assayed for growth inhibition activity. Example 1 describes the examination of a library of exogenous nucleic acid sequences cloned into the IPTG-inducible expression vector pLEX5BA (Krause et al., J. Mol. Biol. 274: 365 (1997)) or a modified version of pLEX5BA, pLEX5BA-3' in which a synthetic linker containing a T7 terminator was ligated between the PstI and HindIII sites of pLEX5BA. In particular, to construct pLEX5BA-3', the following oligonucleotides were annealed and inserted into the PstI and HindIII sites of pLEX5BA:

5'-GTCTAGCATAACCCCTTGGGGCCTCTAAACGGGTCCTTGAGGGGTTTTTTGA-3' (SEQ ID NO: 480)

20 5'-AGCTTCAAAAAACCCCTCAAGGACCCGTTTAGAGGCCCCAAGGGGTTAT GCTAGACTGCA-3' (SEQ ID NO: 481)

Random fragments of *E. coli* genomic DNA were generated by DNAseI digestion or sonication, filled in with T4 polymerase, and cloned into the SmaI site of pLEX5BA or pLEX5BA-3'. Upon activation or induction, the expression vectors produced an RNA molecule corresponding to the subcloned exogenous nucleic acid sequences. The RNA product was in an antisense orientation with respect to the *E. coli* genes from which it was originally derived. This antisense RNA then interacted with sense mRNA produced from various *E. coli* genes and interfered with or inhibited the translation of the sense messenger RNA (mRNA) thus preventing protein production from these sense mRNA molecules. In cases where the sense mRNA encoded a protein required for the proliferation, bacterial cells containing an activated expression vector failed to grow or grew at a substantially reduced rate. Similar results have also been obtained in cases where the gene encodes a non-translated RNA, such as a ribosomal RNA.

It will be appreciated that vectors other than pLEX5BA or pLEX5BA-3' may be used to transcribe the genomic DNA inserts. In addition, it will be appreciated that, if desired, pLEX5BA or pLEX5BA-3' may be modified to introduce features such as stop codons in all three reading frames downstream of the genomic DNA inserts to ensure that if the genomic DNA insert encodes a polypeptide (i.e. the insert is in the sense orientation rather than the antisense orientation or the

insert is in the antisense orientation but contains a cryptic ORF) translation of the polypeptide will terminate shortly after the genomic insert.

EXAMPLE 1

Inhibition of Bacterial Proliferation after IPTG induction

To study the effects of transcriptional induction in liquid medium, growth curves were carried out by back diluting cultures 1:200 into fresh media with or without 1 mM IPTG and measuring the OD_{450} every 30 minutes (min). To study the effects of transcriptional induction on solid medium, 10^2 , 10^3 , 10^4 , 10^5 , 10^6 , 10^7 and 10^8 fold dilutions of overnight cultures were prepared. Aliquots of from 0.5 to 3 μ l of these dilutions were spotted on selective agar plates with or without 1 mM IPTG. After overnight incubation, the plates were compared to assess the sensitivity of the clones to IPTG.

Of the numerous clones tested, some clones were identified as containing a sequence that inhibited *E. coli* growth after IPTG induction. Accordingly, the gene to which the inserted nucleic acid sequence corresponds, or a gene within the operon containing the inserted nucleic acid, may be required for proliferation in *E. coli*.

Characterization of Isolated Clones Negatively Affecting E. coli Proliferation

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Following the identification of those inserts that, upon expression, negatively impacted *E. coli* growth or proliferation, the inserts were isolated and subjected to nucleic acid sequence determination.

EXAMPLE 2

Nucleic Acid Sequence Determination of Identified Clones Expressing Nucleic Acid Fragments with Detrimental Effects of E. coli Proliferation

The nucleotide sequences for the exogenous identified sequences were determined using plasmid DNA isolated using QIAPREP (Qiagen, Valencia, CA) and methods supplied by the manufacturer. The primers used for sequencing the inserts were 5' - TGTTTATCAGACCGCTT - 3' (SEQ ID NO: 1) and 5' - ACAATTTCACACAGCCTC - 3' (SEQ ID NO: 2). These sequences flank the polylinker in pLEX5BA. Sequence identification numbers (SEQ ID NOs) for the identified inserts are listed in Table I and discussed below.

EXAMPLE 3

Comparison Of Isolated Sequences to Known Sequences

The nucleic acid sequences of the subcloned fragments obtained from the expression vectors discussed above were compared to known *E. coli* sequences in GenBank using BLAST version 1.4 or version 2.0.6 using the following default parameters: Filtering off, cost to open a gap=5, cost to extend a gap=2, penalty for a mismatch in the blast portion of run=3, reward for a match in the blast portion of run=1, expectation value (e)=10.0, word size=11, number of one-line descriptions=100, number of alignments to show (B)=100. BLAST is described in Altschul, J Mol Biol. 215:403-10 (1990). Expression vectors were found to contain nucleic acid sequences in both the sense and antisense orientations. The presence of known genes, open reading frames, and ribosome binding sites was determined by comparison to public databases holding genetic information and various computer

programs such as the Genetics Computer Group programs FRAMES and CODONPREFERENCE. Clones were designated as "antisense" if the cloned fragment was oriented to the promoter such that the RNA transcript produced was complementary to the expressed mRNA (or non-translated RNA) from a chromosomal locus. Clones were designated as "sense" if they coded for an RNA fragment that was identical to a portion of a wild type mRNA from a chromosomal locus.

The sequences described in Examples 1-2 that inhibited bacterial proliferation and contained gene fragments in an antisense orientation are listed in Table I. This table lists each identified sequence by: a sequence identification number, a Molecule Number; a gene to which the identified sequence corresponds, listed according to the National Center for Biotechnology Information (NCBI), Blattner (Science 277:1453-1474(1997); also contains the *E. coli* K-12 genome sequence), or Rudd (Micro. and Mol. Rev. 62:985-1019 (1998)), nomenclatures. The CONTIG numbers for each identified sequence is shown, as well as the location of the first and last base pairs located on the *E. coli* chromosome. A Molecule Number with a "**" indicates a clone corresponding to an intergenic sequence.

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<u>TABLE I</u>

Identified Clones with Corresponding Genes and Operons

	Molecule	1			F	Gene name	Gene name
SeqID	Number	Clone name	Contig	start	stop	(Blattner)	(NCBI)
1	EcXA118a	E1M10000131C06	AE000408	5299	5440	b3310	rplN
2	EcXA118b	E1M10000152F04	AE000408	5300	5452	b3310	rplN
3	EcXA118c	E1M10000152H04	AE000408	5311	5450	b3310	rplN
4	EcXA118d	E1M10000153H03	AE000408	5299	5475	b3310	rplN
5	EcXA119	E1M10000129F10	AE000372	2407	2153	b2883	b2883
6	EcXA120	E1M10000129G04	AE000248	2494	2888	b1509	b1509
7	EcXA121	E1M10000119D03	AE000491	1722	2001	b4191	yjfQ
8	EcXA122a	1029-M5	AE000300	232	1	b2108	yehA
			AE000299	10036	9848	b2107	b2107
9	EcXA122b	X3S208-17	AE000300	186	1	b2108	yehA
			AE000299	10036	9870	b2107	b2107
10	EcXA122c	E1M10000124C07	AE000299	10036	9896	b2107	b2107
			AE000300	78	1	b2108	yehA
11	EcXA122d	E1M10000125D06	AE000300	203	1	b2108	yehA
			AE000299	10036	9892	b2107	b2107
12	EcXA123	E1M10000106A08	AE000410	7832	7968	b3343	yheL
13	EcXA124	E1M10000106D02	AE000408	5951	6225	b3311	rpsQ
			AE000408	5951	6225	b3312	rpmC
14	EcXA125	E1M10000124D09	AE000465	7071	7309	b3901	yiiL
15	EcXA126	E1M10000124E02	AE000441	9429	9316	b3644	yicC
16	EcXA127a	E1M10000124E06	AE000369	1145	856	b2851	b2851
17	EcXA127b	E1M10000159A11	AE000369	1145	763	b2851	b2851
18	EcXA128	E1M10000124G04	AE000171	6676	6427	ь0679	nagE
19	EcXA129	E1M10000127C09	AE000123	1270	1506	b0135, b0136	yadC, yadK
20	EcXA130	E1M10000146E05	AE000450	9592	9828	b3737, b3738	atpE, atpB
21	EcXA131	E1M10000162C01	AE000383	11211	11350	b3016	b3016

SeqID	Molecule Number	Clone name	Contig	start	stop	Gene name (Blattner)	Gene name (NCBI)
22	EcXA132	E1M10000163A04	AE000243	5440		b1465	narV
23	EcXA133a	E1M10000120F06	AE000408	5273		b3309, b3310	rplX, rplN
24	EcXA133b	E1M10000132H04	AE000408	5263		b3309, b3310	rplX, rplN
25	EcXA133c	E1M10000172C05	AE000408	5190		b3309, b3310	rplX, rplN
26	EcXA134	E1M10000162H06	AE000402	4689		b3229	sspA
27	EcXA136a	E1M10000147B03	AE000373	11000		b2892	recJ
20	E-VA12Ch	E13 (10000166E04	AE000372	11967		b2891	prfB
28	EcXA136b	E1M10000155F04	AE000373	12222		b2892	recJ
29	EcXA137	E13410000140E10	AE000372	12002	12144		prfB
30		E1M10000142F12	AE000132	9172		b0243, b0244	proA, thrW
31	EcXA138	E1M10000148B09 E1M10000143A12	AE000393	10354	_	b3121	yhaC
32	EcXA139 EcXA139b	E1M10000143A12	AE000189	3600		b0874 b0874	b0874
33	EcXA140a	E1M10000169H02	AE000189 AE000445	3646			b0874
33	ECAA 140a	E11V110000143C10		12573		b3672	b3672
34	EcXA140b	E1M10000151F10	AE000444 AE000445		12697	b3672	ilvB
34	ECAA1400	EIMIOOOTTIFIO	AE000443	12576	12697		b3672
35	EcXA141	E1M10000143G09	AE000294	9227		b2035	ilvB rfc
36	EcXA141	E1M10000143G09	AE000294 AE000408	1		b3299	<u> </u>
	ECAR142	E1W10000139C10	AE000407	10488	10601		rpmJ
37	EcXA143	E1M10000159F03	AE000368	7705		b2846	rpsM b2846
38	EcXA144a	E1M10000160A03	AE000257	545		b1613	manA
39	EcXA144b	E1M10000130F02	AE000257	585		b1613	manA
40	EcXA144c	E1M10000153E04	AE000257	552		b1613	manA
41	EcXA145	E1M10000159204	AE000366	5350		b2827	thyA
42	EcXA146	E1M10000160C02	AE000449	9694		b3725	pstB
43	EcXA147	E1M10000160C03	AE000211	6964		b1111	b1111
44	EcXA148	E1M10000160E10	AE000455	10737	10577	b3794	rffM
45	EcXA149a	E1M10000160F11	AE000374	7930		b2912	ygfA
46	EcXA149b	E1M10000153F05	AE000374	7910		b2912	ygfA
47	EcXA150	E1M10000160H03	AE000442	5556	5377	b3650	spoT
48	EcXA151	E1M10000144E03	AE000429	8099		b3528	dctA
49	EcXA152	E1M10000144G07	AE000308	1086		b2182	bcr
50	EcXA153	E1M10000144B01	AE000477	4261		b4038	yjbI
51	EcXA154	E1M10000150E02	AE000290	5618	5406	b1983	b1983
52	EcXA155	E1M10000150E06	AE000339	116	496	b2522	sseB
53	EcXA156	E1M10000156B08	AE000463	2852	2699	b3874	yihN
54	EcXA157	E1M10000156D07	AE000408	7274	7464	b3314, b3315	rpsC, rplV
.55	EcXA158	E1M10000156G12	AE000338	5181	5370	b2519	b2519
56	EcXA159	E1M10000151G10	AE000154	7217	7618	b0482	b0482
57	EcXA160	E1M10000166G06	AE000269	4488		b1744	b1744
58	EcXA161	869.A23	AE000146	3702		b0398	sbcD
59	EcXA162	E1M10000112F05	AE000497	7921		b4267	yjgV
60	EcXA163	E1M10000118B05	AE000447	8832		b3705	yidC
61	EcXA164	E1M10000118C04	AE000314	6749		b2243	glpC
62	EcXA165	E1M10000118C05	AE000170	219		b0655	ybeJ
63	EcXA166	E1M10000118G06	AE000461	5835		b3859	yihE
64	EcXA167	E1M10000119A05	AE000298	9388		b2093	gatB
65	EcXA168	E1M10000123E09	AE000267	4622		b1721	b1721
66	EcXA169	E1M10000123F11	AE000408	2650		b3303	rpsE
67	EcXA170	E1M10000129G01	AE000143	3523	3913	b0363	ь0363
68	EcXA171	E1M10000132G08	AE000189	6799		b0876	b0876
69	EcXA172	E1M10000139B11	AE000323	3697	3531	b2345	b2345
70	EcXA173	E1M10000153A09	AE000424	6886	6968	b3485	yhhJ

SeqID	Molecule Number	Clone name	Contig	start	stop	Gene name (Blattner)	Gene name (NCBI)
71	EcXA174	E1M10000153C04	AE000377	8932	8832	b2945	endA
72	EcXA175	E1M10000154F03	AE000279	7957	7837	b1854	pykA
73	EcXA176	E1M10000157B02	AE000485	4932	5094	b4125	yjdH
74	EcXA177	E1M10000160H05	AE000326	3140	3035	b2378	b2378
75	EcXA178	E1M10000163H01	AE000113	1	266	b0023	rpsT
76	EcXA179	E1M10000164G04	AE000262	233	1	b1665	valV
77	EcXA180	E1M10000168F02	AE000480	3110	3350	b4066	yjcF
78	EcXA181	E1M10000169D08	AE000469	10535	10604	b3956	ppc
79	EcXA182	E1M10000169H07	AE000376	10447	10586	b2935	tktA
80	EcXA183	E1M10000169H08	AE000118	8416	8228	ь0084	ftsI
81	EcXA184	E1M10000172C01	AE000358	8498	8844	b2750	cysC
82	EcXA185	E1M10000176C01	AE000407	10053	10119	b3297	rpsK
83	EcXA186	E1M10000176F01	AE000135	987	812	ь0270	yagG
84	EcXA187	P319-3.M16	AE000317	2279	1872	b2271	b2271
85	EcXA188	P347.2	AE000211	7845	8005	b1113	b1113
86	EcXA189a	E1M10000168A04	AE000277	2048	1861	b1828	b1828
87	EcXA189b	E1M10000125F09	AE000277	2042	1868	b1828	b1828
88	EcXA189c	E1M10000113F02	AE000277	2050	1857	b1828	b1828
89	EcXA190a	E1M10000161D04	AE000387	49	312	b3052	b3052
90	EcXA190b	E1M10000155B11	AE000387	49	285	b3052	b3052
91	EcXA191a	E1M10000167H09	AE000451	18	220	b3740	gidB
92	EcXA191b	E1M10000120H05	AE000451	1	188	b3740	gidB
93	EcXA192	E1M10000154H07	AE000452	3326	3106	b3750, b3751	rbsC, rpsB

EXAMPLE 4

Identification of Genes and their Corresponding Operons Affected by Antisense Inhibition

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The sequencing of the entire *E. coli* genome is described in Blattner et al., Science 277:1453-1474(1997) and the sequence of the genome is listed in GenBank Accession No.U00096. The operons to which the proliferation-inhibiting nucleic acids correspond were identified using RegulonDB and information in the literature. The coordinates of the boundaries of these operons on the *E. coli* genome are listed in Table III. Table II lists the molecule numbers of the inserts containing the growth inhibiting nucleic acid fragments, the genes in the operons corresponding to the inserts, the SEQ ID NOs of the genes containing the inserts, the SEQ ID NOs of the proteins encoded by the genes, the start and stop points of the genes on the *E. coli* genome, the orientation of the genes on the genome, whether the operons are predicted or documented, and the predicted functions of the genes. The identified operons, their putative functions, and whether or not the genes are presently thought to be required for proliferation are discussed below.

Functions for the identified genes were determined by using either Blattner functional class designations or by comparing identified sequence with known sequences in various databases. A variety of biological functions were noted for the genes to which the clones of the present invention correspond. The functions for the genes of interest appear in Table II.

The proteins that are listed in Table II are involved in a wide range of biological functions.

All Operon Data with Whole Chromosome Coordinates

Maloudo		Esa III	Gog TD					
Number,	Gene	Gene)	(Protein)	Start	Stop	Orientation	oper on prediction	Predicted function
EcXA118a-d	rpmJ	94	287	3440255	3440371	v	documented	50S ribosomal subunit protein X (L36)
	prlA	95	288	3440403	3441734	V		SecY: multispanning membrane protein, translocator of proteins
	Oldr	96	289	3441742	3442176	v		50S ribosomal subunit protein L.15
	TpmD	26	290	3442180	3442359	V		50S ribosomal subunit protein L30
	rpsE	86	291	3442363	3442866	v		eps, spc, spcA; 30S ribosomal subunit protein S5
	rplR	66	292	3442881	3443234	V		50S ribosomal subunit protein L18
	rplF	100	293	3443244	3443777	V		50S ribosomal subunit protein L6;
								gentamicin sensitivity
	rpsH	[101]	294	3443790	3444182	V		30S ribosomal subunit protein S8
	rpsN	701	295	3444216	3444521	v		30S ribosomal subunit protein S14
	rplE	103	296	3444536	3445075	V		50S ribosomal subunit protein L5
	rplX	104	297	3445090	3445404	V		50S ribosomal subunit protein L24
	rplN	105	298	3445415	3445786	V		50S ribosomal subunit protein L14
EcXA119	<i>p</i> 2887	106	299	3022315	3023772	٨	predicted	Unknown
	<i>b</i> 2883	107	300	3023787	3025106	٨		Unknown
	<i>b</i> 2884	108	301	3025142	3025711	٨		Unknown
	b2885	109	302	3025678	3026508	^		Unknown
EcXA120	<i>b1509</i>	110	303	1590689	1592089	V	predicted	Unknown
	ydeK	111	304	1592133	1596110	v		Unknown
EcXA121	yifQ	112	305	4415276	4416031	V	predicted	Unknown
EcXA122	<i>b</i> 2106	113	306	2183937	2184761	^	predicted	Unknown
	<i>b2107</i>	114	307	2184800	2185318	٨		Unknown
	yehA	115	308	2185400	2186434	>	predicted	Unknown
	yehB	116	309	2186450	2188930	V		Unknown

Molecule		Seq ID	Seq ID				operon	
Number	Gene		(Protein)	Start	Stop	Orientation	prediction	Predicted function
	yehC	117	310	2188946	2189665	V		Unknown
	yehD	118	311	2189700	2190242	>		Unknown
EcXA123	yheL	119	312	3472315	3472602	>	predicted	Unknown
	b3344	120	313	3472610	3472969	v		Unknown
	yheN	121	314	3472969	3473355	v		Unknown
	b3346		315	3473355	3474089	V		Unknown
EcXA124	Ösdı	123	316	3445951	3446205	v	documented	documented neaA; 30S ribosomal subunit protein S17
	rpmC	124	317	3446205	3446396	v		50S ribosomal subunit protein L29
	rplP	125	318	3446396	3446806	v		50S ribosomal subunit protein L16
	rpsC	126	319	3446819	3447520	v		30S ribosomal subunit protein S3
	rpIV	127	320	3447538	3447870	v		eryB; erythromycin sensitivity; 50S ribosomal subunit protein L22
	Ssdr	128	321	3447885	3448163	v		30S ribosomal subunit protein S19
	rplB	129	322	3448180	3449001	v		50S ribosomal subunit protein L2
	rplW	130	323	3449019	3449321	v		50S ribosomal subunit protein L23
	TpID	131	324	3449318	3449923	v		eryA; 50S ribosomal subunit protein L4;
								erythromycin sensitivity
	rplC	132	325	3449934	3450563	٧		50S ribosomal subunit protein L3
	rpsJ		326	3450596	3450907	V		nusE; 30S ribosomal subunit protein S10
EcXA125	yiiL	134	327	4090705	4091019	>	predicted	Unknown
EcXA126	yicC		328	3814303	3815166	٨	predicted	Unknown
EcXA127a-b	<i>b</i> 2851	136	329	2989290	2989781	٨	predicted	Unknown
EcXA128	nagE	137	330	703167	705113		documented	pstN; N-acetylglucosamine-specific enzyme II of phosphotransferase system
EcXA129	yadC	138	331	149715	150953	v	predicted	Unknown
	yadK	139	332	151003	151599	>		Unknown
	yadL	140	333	151626	152231	>	•	Unknown
	yadM	141	334	152243	152854	v		Unknown

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Molecule	į		Sed ID		i		operon		
Number	Gene	ne)	(Protein)	Start	Stop	Orientation	prediction	Predicted function	
EcXA130	atpC	142	335	3913181	3913600	٧	documented	papG, uncC; membrane-bound ATP synthase, F1 sector, -subunit (EC 3.6.1.3)	
	atpD	143	336	3913621	3915003	V		papB, uncD; membrane-bound ATP synthase, F1 sector, -subunit (EC 3.6.1.3)	
	atpG	144	337	3915030	3915893	v		papC, uncG; membrane-bound ATP synthase, F1 sector, -subunit (EC 3.6.1.3)	1
	atpA	145	338	3915944	3917485	V	•	papA, uncA; membrane-bound ATP synthase, F1 sector, -subunit (EC 3.6.1.3)	
	Нфт	146	339	3917498	3918031	V		papE, uncH; membrane-bound ATP synthase, F1 sector, -subunit (EC 3.6.1.3)	Ī
	atpF	147	340	3918046	3918516	٧		papF, uncF, membrane-bound ATP synthase, F0 sector, subunit b (EC 3.6.1.3)	
	atpE	148	341	3918578	3918817	٧		papH, uncE; membrane-bound ATP synthase, F0 sector, subunit c; DCCD (EC 3.6.1.3)	
	atpB	149	342	3918864	3919679	V		papD, uncB; membrane-bound ATP synthase, F0 sector, subunit a (EC 3.6.1.3)	
	atpI	150	343	8896168	3920080	٧		uncl; membrane-bound ATP synthase subunit, F1-F0-type proton-ATPase (EC 3.6.1.34)	
EcXA131	b3015 b3016	151 152	344 345	3156944 3158185	3158185 3159162	>	predicted	Unknown Unknown	
EcXA132	narV	153	346	1533961	1534641	V	documented	regulationCryptic nitrate reductase II, - subunit	
	narW	154.	347	1534638	1535333	V		regulation Cryptic nitrate reductase Π , -subunit	
	narY		348	1535333	1536877	>		regulationCryptic NR II, -subunit	П
	narZ	156	349	1536874	1540614	>		regulationCryptic NR II, -subunit	
EcXA133a-c							Same		
							operon as EcXA118		

Molecule		Sea ID	Sed ID				operon	
Number	Gene	(Gene)	(Protein)	Start	Stop	Orientation	prediction	Predicted function
EcXA134	sspB	157	350	3373914	3374411	V	documented	Stress response protein
	sspA	158	351	3374417	3375055	V		pog; stress response protein
EcXA136a-b	Ssyl	159	352	3031677	3033194	V	documented	asuD herC; lysyl tRNA synthetase, constitutive
	prfB	160	353	3033204	3034302	V		supK; peptide chain release factor 2
	recJ	191	354	3034393	3036126	v	predicted	Single-stranded DNA-specific exonuclease, 5-3
	dspC	162	355	3036132	3036842	V		xprA; periplasmic disulfide oxidoreductase, protein disulfide isomerase
	xerD	163	356	3036867	3037763	V		xprB; recombinase, site specific
EcXA137	proB	164	357	259612	260715	٨	documented	pro2; -glutamyl kinase (EC 2.7.2.11)
	proA	165	358	260727	261980	٨		prol; -glutamyl phosphate reductase (EC 1.2.1.41)
EcXA138	yhaB	166	359	3265474	3266034	٨	predicted	
	yhaC	167	360	3266056	3267243	^		
	b0874	168	361	913181	914128	>	predicted	
EcXA140a-b	ilvN	691	362	3848429	3848719	V	documented	Acetohydroxy acid synthase I, small subunit (EC 4.1.3.18); valine sensitive small subunit; positive regulator for thr and ilv
	ilvB	170	363	3848723	3850411	V		Acetolactate synthase I, valine sensitive (EC 4.1.3.18)
	<i>b</i> 3672	171	364	3850517	3850615	V		
EcXA141	yi52_7	172	365	2099917	2100933	V	predicted	nucleotide sequence and phylogenetic relationships of a new E. coli insertion element. Schwartz E
	f	173	366	2100938	2101411	>		Unknown
	yefI	174	367	2101413	2102531	>		Unknown
	Нfəл	175	368	2102516	2103106	>		Unknown

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Morecare	ζ		or hac	č	,		operon	•
Number	Gene	(e)	(Frotein)	Start	Stop	Orientation	prediction	Predicted function
	yefG		369	2103087	2104079	>		Unknown
	rfc		370	2104082	2105248	v		O-antigen polymerase
	yefE	178	371	2105248	2106351	v		Unknown
EcXA142							Same	
			•				operon as EcXA118	
EcXA143	b2846		372	2985498	2986190		predicted	Unknown
EcXA144a-c	manA		373	1686600	1687775	٨	predicted	pmi; mannosephosphate isomerase (EC 5.3.1.8)
EcXA145	thyA	181	374	2962383	2963177	v	documented	Aminopterin, trimethoprim resistance; thymidylate synthetase (EC 2.1.1.45)
	lgt	182	375	2963184	2964059	V		transferaseumpA;
							•	phosphatidylglycerol:prolipoprotein diacylglycerol transferase
EcXA146	Doyd	183	376	3904481	3905206	V	documented	phoT; P uptake, high-affinity P-specific
								transport system, regulatory gene
	pstB		377	3905221	3905994	V		phoT; high-affinity P-specific transport; cytoplasmic ATP-binding protein
	pstA	185	378	3906177	3907067	v		R2pho, phoR2b, phoT; high-affinity P-specific transport
	pstC	981	379	3907067	3908026	v		phoW; high-affinity P-specific transport; cytoplasmic membrane component
	pstS	187	380	3908113	3909153	V		phoR2, nmpA, phoR2a, phoS, R2pho; high-affinity P-specific transport; periplasmic
EcXA147	IIIIq	188	381	1167423	1168133	\ \ \	predicted	Unknown
EcXA148	yifH		382	3972208	3972753	^	predicted	Unknown
	yifI		383	3972758	3973888	^		Unknown
	yifJ		384	3973890		>		Unknown
	rffT	192	385	3976214	3977566	٨		Synthesis of enterobacterial common antigen; Fuc4NAc transferase

Molecule		Seq ID	Seq ID				operon	
Number	Gene		(Protein)	Start	Stop	Orientation	prediction	Predicted function
	rffM	<i>-</i>	386	3977569	3978309	^		UDP-ManNAcA transferase
	b4404		387	3975137	3975361	^		Unknown
	<i>b4405</i>	195	388	3975603	3976217	^		Unknown
a-p	ygfA	196	688	3054261	3054809	<	predicted	Unknown
EcXA150	rpoZ	197	390	3819733	3820008	٨	documented	spoS; RNA polymerase,
	spoT	198	391	3820027	3822135	۸		Guanosine 5 -diphosphate, 3 -diphosphate pyrophosphatase, ppGpp synthetase II activity
	Nods	199	392	3822142	3822831	٨		
	recG	200	393	3822837	3824918	۸		spoV? branch migration of Holliday junctions, junction-specific DNA helicase (see ruvABC)
EcXA151	dctA	201	394	3679791	3681077	V	predicted	Uptake of C-4 dicarboxylic acids; 3-fluoromalate resistance, D-tartrate resistant
EcXA152	bcr	202	395	2276590	2277780	>	predicted	bicA, bicR, sur, suxA; transmembrane; affects sulfathiazole-sulfonamide resistance
	yejD	203	396	2277808	2278503	V		Unknown
EcXA153	yjbI	204	397	4248534	4249862	^	predicted	Unknown
EcXA154	<i>b1983</i>	205	368	2054880	2055596	٨	predicted	Unknown
EcXA155	sseB	206	399	2652177	2652962	>	predicted	Enhances serine sensitivity (inhibits homoserine de Hase) on lactate: weeker than
							·	sseA
9	yihN	207	400	4059826	4061091	٨	predicted	Unknown
EcXA157							Same	Unknown
							operon as EcXA124	
EcXA158	<i>b</i> 2519	208	401	2643033	2645345	>	predicted	Unknown
	<i>b</i> 2520	209	402	2645346	2650307	>		Unknown
EcXA159	b0482	210	403	506510	507304	>	predicted	Unknown

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Molecule		Sed ID	Sed ID				operon	
Number	Gene	(Gепе)	(Protein)	Start	Stop	Orientation	prediction	Predicted function
EcXA160	b1744	211	404	1823979	1824947	V	predicted	Unknown
	b1745	212	405	1824940	1826283	>		Unknown
	b1746	213	406	1826280	1827758	>		Unknown
	b1747	214	407	1827755	1828789	V		Unknown
	b1748	215	408	1828786	1830006	V		Unknown
EcXA161	spcC	216	409	411831	414977	V	predicted	Cosuppressor with sbcB of recB recC mutations
	spcD	217	410	414974	416176	V		Cosuppressor with sbcB of recB recC mutations
EcXA162	yjgU	218	411	4490155	4490919	V	predicted	Unknown
	yjgV	219	412	4490943	4491974	V		Unknown
EcXA163	yidC	220	413	3882705	3884351	^	predicted	Unknown
EcXA164	glpA	221	414	2350667	2352295	^	documented	Glycerol-3-phosphate dehydrogenase (anaerobic) large subunit (EC 1.1.99.5)
	gdj8	222	415	2352285	2353544	^		sn-Glycerol-3-phosphate dehydrogenase
								(anaerobic) subunit (EC 1.1.99.5); membraneanchor
	glpC	223	416	2353541	2354731	٨		sn-Glycerol-3-phosphate dehydrogenase
EcXA165	ybeJ	224	417	686062	026989	V	predicted	Unknown
EcXA166	yihE	225	418	4039996	4040982	^	predicted	Unknown
	dsbA	226	419	4040999	4041625			iarA, ppfA; disulfide oxidoreductase, periplasmic protein disulfide-isomerase; role incytochrome c synthesis (EC 5.3.4.1)
EcXA167	gatR_2	227	420	2169417	2169755	V	documented	
	gatD		421	2169855	2170895	>		Galactitol-1-phosphate dehydrogenase
	gatC		422	2170943	2172298	V		Galactitol-specific enzyme IIC of PTS
	gatB	230	423	2172302	2172586	٧		Galactitol-specific enzyme IIB of PTS

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Molecule Number	Gene	Sed ID (Gene)	Seq 1D (Protein)	Start	Stop	Orientation	operon prediction	Predicted function
	gatA	+	424	2172617	2173069	V		Galactitol-specific enzyme IIA of phosphotransferase system (PTS)
	gatZ		425	2173079	2174341	V		Function unknown
	gatY	233	426	2174370	2175230	V		D-Tagatose-1,6-bisphosphate aldolase
EcXA168	b1720		427	1801118	1801591	٨	predicted	Unknown
	b1721		428	1801602	1803017	٨		Unknown
EcXA169							Same	Unknown
							operon as EcXA118	
EcXA170	b0362		429	381728	382114	V	predicted	Unknown
1	60363		430	381963	383159	V		Unknown
EcXA171	60876		431	915696	917354	٨	predicted	Unknown
EcXA172	<i>b</i> 2345	239	432	2461032	2462090	٨	predicted	Unknown
EcXA173	yhhJ		433	3623310	3624437	V	predicted	Unknown
	b3486	241	434	3624434	3627118	٧		Unknown
	Inhi		435	3627165	3628232	v		Unknown
EcXA174	endA	243	436	3088366	3089073	٨	predicted	DNA-specific endonuclease I; extensive DNA breakdown
EcXA175	pykA	244	437	1935673	1937115	٨	predicted	Pyruvate kinase A (II); (EC 2.7.1.40)
EcXA176	yjdG		438	4346893	4347612	V	predicted	Unknown
	yjdH	246	439	4347609	4349240	v		Unknown
EcXA177	<i>b2378</i>		440	2493599	2494585	٨	predicted	Unknown
EcXA178	rpsT	248	441	20815	21078	Y	predicted	sups20; 30S ribosomal subunit protein S20
EcXA180	yjcF		442	4279362	4280654	>	predicted	Unknown
EcXA181	odd	250	443	4148026	4150677	v	predicted	asp, glu; phosphoenolpyruvate carboxylase (EC 4.1.1.31)
EcXA182	tktA	251	444	3077663	3079654	v	predicted	Transketolase (BC 2.2.1.1)
EcXA183	yabB	252	445	89634	26006	٨	predicted	Unknown
	yabC		446	90094	91035	٨		Unknown

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Monecule Number	Gene	Seq III (Gene)	Seq III (Protein)	Start	Stop	Orientation	operon prediction	Predicted function
	ftsL	$\overline{}$	447	91032	91397	^		sensitiveCell division and growth; essential
								gene; cytoplasmic membrane protein
	ftsI	255	448	91413	93179	٨		sensitivepbpB, sep; peptidoglycan
								synthetase; penicillin-binding protein 3
	murE		449	93166	94653	<		meso-Diaminopimelate adding enzyme
	murF		450	94650	80096	^		mra; D-alanyl:D-alanine adding enzyme
	mraY	258	451	70096	97084	^		UDP-N-acetylmuramoyl-
								pentapeptide:undecaprenyl-PO4 phosphatase (EC 2.7.8.13)
	murD	259	452	78076	98403	٨		UDP-N-acetylmuramoyl-L-alanine:D-
								glutamate ligase (EC 6.3.2.9)
	ftsW	760	453	98403	99647	<		sensitiveCytoplasmic membrane required for
								PBP 2 expression; homology to rodA
	murG	261	454	99644	100711	<		UDP-NAc-glucosamine: NAc-muramyl-
								(pentapeptide) pyrophosphoryl-
								undecaprenolNAc-glucosamine transferase
	murC	262	455	100765	102240	^		L-Alanine adding enzyme
	ddlB		456	102233	103153	<		ddl; D-Alanine: D-alanine ligase
EcXA184	cysC	264	457	2871410	2872015	>	documented	Adenylylsulfate kinase (EC 2.7.1.25)
	cysN	265	458	2872015	2873442	\ \ \		ATP sulfurylase (ATP:sulfate
								adenylyltransferase)
EcXA185	\mathcal{Z}_{ld}	266	459	3437253	3437636	>	documented	50S ribosomal subunit protein L17
		1		, , ,				
	rpoA	267	460	3437677	3438666	, V		phs, sez; phage P2 vir1 resistance; RNA polymerase, -subunit (EC 2.7.7.6).
	DsD	268	461	3438692	3439312	V		ramA, sud2; 30S ribosomal subunit protein S4
	rpsK		462	3439346	3439735	>		30S ribosomal subunit protein S11
	rpsM	270	463	3439752	3440108	V		30S ribosomal subunit protein S13
EcXA186	yagG		464	284619	286001	^	predicted	Unknown

Molecule		Seq ID	Seq ID				operon	
Number	Gene	(Gene) (Prote	ein)	Start	Stop	Orientation	prediction	Predicted function
	b0271	272		286013	287623	^		Unknown
EcXA187	b2271	273	466	2383874	2384851	^	predicted	Unknown
EcXA188	<i>b1113</i>	274	467	1168635	1169597	>	predicted	Unknown
EcXA189a-c	b1828	275	468	1908189	1909673	٨	predicted	Unknown
EcXA190a-b	b3052	276	469	3192961	3194394	v	predicted	Unknown
	glnE	277	470	3194442	3197282	V		GS adenylyl transferase (EC 2.7.7.42)
	ygiF	278		3197305	3198606	>		Unknown
EcXA191a-b	gidB	279	472	3920685	3921308		predicted	Glucose effects on cell division, perhaps
								replication
	gidA	280	473	3921372	3923261	v		Glucose effects on cell division, perhaps
								replication
	mioC	281	474	3923640	3924083	V		Initiation of replication; transcription of 16- kDa protein proceeds through ori
EcXA192	rbsD	282	475	3930941	3931396		documented	documented rbsP; D-ribose high-affinity transport system
	rbsA	283	476	3931404	3932909	^		rbsP, rbsT; D-ribose high-affinity transport
								system (may have chemotaxis function)
	rbsC	284	477	3932914	3933879			rbsP, rbsT; D-ribose high-affinity transport
		•						system
	rbsB	285	478	3933904	3934794	٨		prIB, rbsP, D-ribose periplasmic binding protein
	rbsK	286	479	3934920	3935849	^		Ribokinase (BC 2.7.1.15)

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Functions for the identified genes were assigned using either Blattner functional class designations, functions referenced in Berlyn, MKB "Linkage Map of Escherichia coli K-12, Edition 10: The Traditional Map". (1998) Microbiol. Mol. Biol. Rev. September 62 (3): 814-984, or by comparing identified sequence with known sequences in various databases. A variety of biological functions were noted for the genes to which the clones of the present invention correspond. Biological functions for genes that lie on the same operon as an identified gene have also been made. The functions for the genes of interest appear in Table II.

The genes of interest have a variety of biological functions. For example, genes that are thought to function as transport or binding proteins, that participate in translation or post-translational modification, that are involved in carbon compound catabolism, that are thought to be enzymes, participate in cell processes, energy metabolism and biosynthetic functions appear in Table II. Genes that are involved in cell structure, transcription, RNA processing and degradation also appear in Table II.

Several of the expression vectors contain fragments that correspond to genes of unknown function or if the function is known, it is not known whether the gene is essential. For example, EcXA119, 120, 121, 122a-d, 123, 125, 126, 127a-b, 128, 129, 131, 132, 138, 139a-b, 141, 143, 146, 147, 14, 149a-b, 152, 153, 154, 155, 156, 158, 159, 160, 162, 163, 164, 165, 166, 167, 168, 170, 171, 172, 173, 176, 177, 180, 181, 186, 187, 188, 189a-b, 190a-b, 191a-b, and 192 are all exogenous nucleic acid sequences that correspond to *E. coli* proteins that have no known function or where the function has not been shown to be essential or nonessential.

The present invention reports a number of novel *E. coli* genes and operons that are required for proliferation. From the list of clone sequences identified here, each was identified to be a portion of a gene in an operon required for the proliferation of *E. coli*. Cloned sequences corresponding to genes already known to be required for proliferation in *E. coli* include EcXA118a-d, 124, 130, 133a-c, 136a-b, 142, 145, 150, 157, 169, 178, 182, 183 and 185 are exogenous nucleic acid sequences that correspond to *E. coli* genes that are known to be required for cellular proliferation. The remaining identified sequences correspond to *E. coli* genes previously undesignated as required for proliferation in the art.

An interesting observation of the present invention is that there are also several sequence fragments that correspond to *E. coli* genes that are not thought to be required for *E. coli* proliferation. Nevertheless, under the conditions described above, the antisense expression of these gene fragments causes a reduction in cell growth. This result implies that the genes corresponding to the identified sequences are actually required for proliferation or are in operons required for proliferation. Molecule Nos. corresponding to these genes are EcXA128, 134, 137, 140a-b, 144a-c, 151, 161, 174, 175, and 184.

Following identification of the sequences of interest, these sequences were localized into operons. Since bacterial genes are expressed in a polycistronic manner, the antisense inhibition of a

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single gene in an operon might effect the expression of all the other genes on the operon or the genes down stream from the single gene identified. In order to determine which of the gene products in an operon are required for proliferation, each of the genes contained within an operon may be analyzed for their effect on viability as described below.

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TABLE III

Operon Boundaries

Molecule Number	Start	Stop
EcXA118a-d	3440255	3445786
EcXA119	3022315	3026508
EcXA120	1590689	1596110
EcXA121	4415276	4416031
EcXA122	2183937	2190242
EcXA123	3472315	3474089
EcXA124	3445951	3450907
EcXA125	4090705	4091019
EcXA126	3814303	3815166
EcXA127a-b	2989290	2989781
EcXA128	703167	705113
EcXA129	149715	152854
EcXA130	3913181	3920080
EcXA131	3156944	3159162
EcXA132	1533961	1540614
EcXA133a-c	Same operon as	
·	EcXA118	
EcXA134	3373914	3375055
EcXA136a-b	3031677	3037763
EcXA137	259612	261980
EcXA138	3265474	3267243
EcXA139a-b	913181	914128
EcXA140a-b	3848429	3850615
EcXA141	2099917	2106351
EcXA142	Same operon as	
	EcXA118	
EcXA143	2985498	2986190
EcXA144a-c	1686600	1687775
EcXA145	2962383	2964059
EcXA146	3904481	3909153
EcXA147	1167423	1168133
EcXA148	3972208	3976217
EcXA149a-b	3054261	3054809
EcXA150	3819733	3824918
EcXA151	3679791	3681077
EcXA152	2276590	2278503
EcXA153	4248534	4249862
EcXA154	2054880	2055596
EcXA155	2652177	2652962
EcXA156	4059826	4061091
EcXA157	Same operon as	

Molecule Number	Start	Stop
	EcXA124	
EcXA158	2643033	2645345
	2645346	2650307
EcXA159	506510	507304
EcXA160	1823979	1830006
EcXA161	411831	416176
EcXA162	4490155	4491974
EcXA163	3882705	3884351
EcXA164	2350667	2354731
EcXA165	686062	686970
EcXA166	4039996	4041625
EcXA167	2169417	2175230
EcXA168	1801118	. 1803017
EcXA169	Same operon as	
	EcXA118	
EcXA170	381728	383159
EcXA171	915696	917354
EcXA172	2461032	2462090
EcXA173	3623310	3628232
EcXA174	3088366	3089073
EcXA175	1935673	1937115
EcXA176	4346893	4349240
EcXA177	2493599	2494585
EcXA178	20815	21078
EcXA180	4279362	4280654
EcXA181	4148026	4150677
EcXA182	3077663	3079654
EcXA183	89634	103153
EcXA184	2871410	2873442
EcXA185	3437253	3440108
EcXA186	284619	287623
EcXA187	2383874	2384851
EcXA188	1168635	1169597
EcXA189a-c	1908189	1909673
EcXA190a-b	3192961	3198606
EcXA191a-b	3920685	3924083
EcXA192	3930941	3935849

EXAMPLE 5

Identification of Individual Genes within an Operon Required for Proliferation

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The following example illustrates a method for determining which gene in an operon is required for proliferation. The clone insert corresponding to Molecule No. EcXA119 possesses nucleic acid sequence homology to the *E. coli* gene *b2883*. This gene is located in an operon containing the *b2882*, *b2883*, *b2884*, and *b2885* genes. To determine which gene or genes in this operon are required for proliferation, each gene is selectively inactivated using homologous recombination. Gene *b2885* is the first gene to be inactivated.

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Deletion inactivation of a chromosomal copy of a gene in *E. coli* can be accomplished by integrative gene replacement. The principle of this method (Hamilton, C. M., et al 1989. *J. Bacteriol.* 171: 4617-4622) is to construct a mutant allele of the targeted gene, introduce that allele into the chromosome using a conditional suicide vector, and then force the removal of the native wild type allele and vector sequences. This will replace the native gene with a desired mutation(s) but leave promoters, operators, etc. intact. Essentiality of a gene is determined either by deduction from genetic analysis or by conditional expression of a wild type copy of the targeted gene (trans complementation).

The first step is to generate a mutant b2885 allele using PCR amplification. Two sets of PCR primers are chosen to produce a copy of b2885 with a large central deletion to inactivate the gene. In order to eliminate polar effects, it is desirable to construct a mutant allele comprising an in-frame deletion of most or all of the coding region of the b2885 gene. Each set of PCR primers is chosen such that a region flanking the gene to be amplified is sufficiently long to allow recombination (typically at least 500 nucleotides on each side of the deletion). The targeted deletion or mutation will be contained within this fragment. To facilitate cloning of the PCR product, the PCR primers may also contain restriction endonuclease sites found in the cloning region of a conditional knockout vector such as pKO3 (Link, et al 1997 J. Bacteriol. 179 (20): 6228-6237). Suitable sites include Notl, Sall, BamHI and Smal. The b2885 gene fragments are produced using standard PCR conditions including, but not limited to, those outlined in the manufacturers directions for the Hot Start Taq PCR kit (Qiagen, Inc., Valencia, CA). The PCR reactions will produce two fragments that can be fused together. Alternatively, crossover PCR can be used to generate a desired deletion in one step (Ho, S. N., et al 1989. Gene 77: 51-59, Horton, R. M., et al 1989, Gene 77: 61-68). The mutant allele thus produced is called a "null" allele because it cannot produce a functional gene product.

The mutant allele obtained from PCR amplification is cloned into the multiple cloning site of pKO3. Directional cloning of the *b2885* null allele is not necessary. The pKO3 vector has a temperature-sensitive origin of replication derived from pSC101. Therefore, clones are propagated at the permissive temperature of 30°C. The vector also contains two selectable marker genes: one that confers resistance to chloramphenical and another, the *Bacillus subtilis sacB* gene, that allows for counter-selection on sucrose containing growth medium. Clones that contain vector DNA with the null allele inserted are confirmed by restriction endonuclease analysis and DNA sequence analysis of isolated plasmid DNA. The plasmid containing the *b2885* null allele insert is known as a knockout plasmid.

Once the knockout plasmid has been constructed and its sequence verified, it is transformed into a Rec⁺ E. coli host cell. Transformation can be by any standard method such as electroporation. In some fraction of the transformed cells, plasmids will integrate into the E. coli chromosome by homologous recombination between the b2885 null allele in the plasmid and the

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b2885 gene in the chromosome. Transformant colonies in which such an event has occurred are readily selected by growth at the non-permissive temperature of 43°C and in the presence of choramphenicol. At this temperature, the plasmid will not replicate as an episome and will be lost from cells as they grow and divide. These cells are no longer resistant to chloramphenicol and will not grow when it is present. However, cells in which the knockout plasmid has integrated into the *E. coli* chromosome remain resistant to chloramphenicol and propagate.

Cells containing integrated knock-out plasmids are usually the result of a single crossover event that creates a tandem repeat of the mutant and native wild type alleles of b2885 separated by the vector sequences. A consequence of this is that b2885 will still be expressed in these cells. In order to determine if the gene is essential for growth, the wild type copy must be removed. This is accomplished by selecting for plasmid excision, a process in which homologous recombination between the two alleles results in looping out of the plasmid sequences. Cells that have undergone such an excision event and have lost plasmid sequences including sacB gene are selected for by addition of sucrose to the medium. The sacB gene product converts sucrose to a toxic molecule. Thus counter selection with sucrose ensures that plasmid sequences are no longer present in the cell. Loss of plasmid sequences is further confirmed by testing for sensitivity to chloramphenicol (loss of the chloramphenicol resistance gene). The latter test is important because occasionally a mutation in the sacB gene can occur resulting in a loss of sacB function with no effect on plasmid replication (Link, et. al., 1997 J. Bacteriol. 179 (20): 6228-6237). These artifact clones retain plasmid sequences and are therefore still resistant to chloramphenicol.

In the process of plasmid excision, one of the two b2885 alleles is lost from the chromosome along with the plasmid DNA. In general, it is equally likely that the null allele or the wild type allele will be lost. Therefore, if the b2885 gene is not essential, half of the clones obtained in this experiment will have the wild type allele on the chromosome and half will have the null allele. However, if the b2885 gene is essential, cells containing the null allele will not be obtained as a single copy of the null allele would be lethal.

To determine the essentiality of b2885, a statistically significant number of the resulting clones, at least 20, are analyzed by PCR amplification of the b2885 gene. Since the null allele is missing a significant portion of the b2885 gene, its PCR product is significantly shorter than that of the wild type gene and the two are readily distinguished by gel electrophoretic analysis. The PCR products may also be subjected to sequence determination for further confirmation by methods well known to those in the art.

The above experiment is generally adequate for determining the essentiality of a gene such as b2885. However, it may be necessary or desirable to more directly confirm the essentiality of the gene. There are several methods by which this can be accomplished. In general, these involve three steps: 1) construction of an episome containing a wild type allele, 2) isolation of clones containing a single chromosomal copy of the mutant null allele as described above but in the

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presence of the episomal wild type allele, and then 3) determining if the cells survive when the expression of the episomal allele is shut off. In this case, the trans copy of wild type b2885 is made by PCR cloning of the entire coding region of b2885 and inserting it in the sense orientation downstream of an inducible promoter such as the E. coli lac promoter. Transcription of this allele of b2885 will be induced in the presence of IPTG which inactivates the lac repressor. Under IPTG induction b2885 protein will be expressed as long as the recombinant gene also possesses a ribosomal binding site, also known as a "Shine-Dalgarno Sequence". The trans copy of b2885 is cloned on a plasmid that is compatible with pSC101. Compatible vectors include p15A, pBR322, and the pUC plasmids, among others. Replication of the compatible plasmid will not be temperature-sensitive. The entire process of integrating the null allele of b2885 and subsequent plasmid excision is carried out in the presence of IPTG to ensure the expression of functional b2885 protein is maintained throughout. After the null b2885 allele is confirmed as integrated on the chromosome in place of the wild type b2885 allele, then IPTG is withdrawn and expression of functional b2885 protein shut off. If the b2885 gene is essential, cells will cease to proliferate under these conditions. However, if the b2885 gene is not essential, cells will continue to proliferate under these conditions. In this experiment, essentiality is determined by conditional expression of a wild type copy of the gene rather than inability to obtain the intended chromosomal disruption.

An advantage of this method over some other gene disruption techniques is that the targeted gene can be deleted or mutated without the introduction of large segments of foreign DNA. Therefore, polar effects on downstream genes are eliminated or minimized. There are methods described to introduce inducible promoters upstream of potential essential bacterial genes. However in such cases, polarity from multiple transcription start points can be a problem. One way of preventing this is to insert a gene disruption cassette that contains strong transcriptional terminators upstream of the integrated inducible promoter (Zhang, Y, and Cronan, J. E. 1996 J. Bacteriol. 178 (12): 3614-3620). The described techniques will all be familiar to one of ordinary skill in the art.

Following the analysis of the b2885 gene, the other genes of the operon are investigated to determine if they are required for proliferation.

EXAMPLE 6

Expression of the Proteins Encoded by Genes Identified as Required for E. coli Proliferation

The following is provided as one exemplary method to express the proliferation-required proteins encoded by the identified sequences described above. First, the initiation and termination codons for the gene are identified. If desired, methods for improving translation or expression of the protein are well known in the art. For example, if the nucleic acid encoding the polypeptide to be expressed lacks a methionine codon to serve as the initiation site, a strong Shine-Delgarno sequence, or a stop codon, these sequences can be added. Similarly, if the identified nucleic acid sequence lacks a

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transcription termination signal, this sequence can be added to the construct by, for example, splicing out such a sequence from an appropriate donor sequence. In addition, the coding sequence may be operably linked to a strong promoter or an inducible promoter if desired. The identified nucleic acid sequence or portion thereof encoding the polypeptide to be expressed is obtained by PCR from the bacterial expression vector or genome using oligonucleotide primers complementary to the identified nucleic acid sequence or portion thereof and containing restriction endonuclease sequences for *NcoI* incorporated into the 5' primer and *BgIII* at the 5' end of the corresponding 3'-primer, taking care to ensure that the identified nucleic acid sequence is positioned in frame with the termination signal. The purified fragment obtained from the resulting PCR reaction is digested with *NcoI* and *BgIII*, purified and ligated to an expression vector.

The ligated product is transformed into DH5\alpha or some other *E. coli* strain suitable for the over expression of potential proteins. Transformation protocols are well known in the art. For example, transformation protocols are described in: Current Protocols in Molecular Biology, Vol. 1, Unit 1.8, (Ausubel, et al., Eds.) John Wiley & Sons, Inc. (1997). Positive transformants are selected after growing the transformed cells on plates containing 50-100 µg/ml Ampicillin (Sigma, St. Louis, Missouri). In one embodiment, the expressed protein is held in the cytoplasm of the host organism. In an alternate embodiment, the expressed protein is released into the culture medium. In still another alternative, the expressed protein can be sequestered in the periplasmic space and liberated therefrom using any one of a number of cell lysis techniques known in the art. For example, the osmotic shock cell lysis method described in Chapter 16 of Current Protocols in Molecular Biology, Vol. 2, (Ausubel, et al., Eds.) John Wiley & Sons, Inc. (1997). Each of these procedures can be used to express a proliferation-required protein.

Expressed proteins, whether in the culture medium or liberated from the periplasmic space or the cytoplasm, are then purified or enriched from the supernatant using conventional techniques such as ammonium sulfate precipitation, standard chromatography, immunoprecipitation, immunochromatography, size exclusion chromatography, ion exchange chromatography, and HPLC. Alternatively, the secreted protein can be in a sufficiently enriched or pure state in the supernatant or growth media of the host to permit it to be used for its intended purpose without further enrichment. The purity of the protein product obtained can be assessed using techniques such as Coomassie or silver staining or using antibodies against the control protein. Coomassie and silver staining techniques are familiar to those skilled in the art.

Antibodies capable of specifically recognizing the protein of interest can be generated using synthetic peptides using methods well known in the art. See, Antibodies: A Laboratory Manual, (Harlow and Lane, Eds.) Cold Spring Harbor Laboratory (1988). For example, 15-mer peptides having a sequence encoded by the appropriate identified gene sequence of interest or portion thereof can be chemically synthesized. The synthetic peptides are injected into mice to generate antibodies to the polypeptide encoded by the identified nucleic acid sequence of interest or portion thereof.

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Alternatively, samples of the protein expressed from the expression vectors discussed above can be purified and subjected to amino acid sequencing analysis to confirm the identity of the recombinantly expressed protein and subsequently used to raise antibodies. An Example describing in detail the generation of monoclonal and polyclonal antibodies appears in Example 7.

The protein encoded by the identified nucleic acid sequence of interest or portion thereof can be purified using standard immunochromatography techniques. In such procedures, a solution containing the secreted protein, such as the culture medium or a cell extract, is applied to a column having antibodies against the secreted protein attached to the chromatography matrix. The secreted protein is allowed to bind the immunochromatography column. Thereafter, the column is washed to remove non-specifically bound proteins. The specifically bound secreted protein is then released from the column and recovered using standard techniques. These procedures are well known in the art.

In an alternative protein purification scheme, the identified nucleic acid sequence of interest or portion thereof can be incorporated into expression vectors designed for use in purification schemes employing chimeric polypeptides. In such strategies the coding sequence of the identified nucleic acid sequence of interest or portion thereof is inserted in-frame with the gene encoding the other half of the chimera. The other half of the chimera can be maltose binding protein (MBP) or a nickel binding polypeptide encoding sequence. A chromatography matrix having antibody to MBP or nickel attached thereto is then used to purify the chimeric protein. Protease cleavage sites can be engineered between the MBP gene or the nickel binding polypeptide and the identified expected gene of interest, or portion thereof. Thus, the two polypeptides of the chimera can be separated from one another by protease digestion.

One useful expression vector for generating maltose binding protein fusion proteins is pMAL (New England Biolabs), which encodes the *malE* gene. In the pMal protein fusion system, the cloned gene is inserted into a pMal vector downstream from the *malE* gene. This results in the expression of an MBP-fusion protein. The fusion protein is purified by affinity chromatography. These techniques as described are well known to those skilled in the art of molecular biology.

EXAMPLE 7

Production of an Antibody to an isolated E. coli Protein

Substantially pure protein or polypeptide is isolated from the transformed cells as described in Example 6. The concentration of protein in the final preparation is adjusted, for example, by concentration on a 10,000 molecular weight cut off AMICON filter device (Millipore, Bedford, MA), to the level of a few micrograms/ml. Monoclonal or polyclonal antibody to the protein can then be prepared as follows:

Monoclonal Antibody Production by Hybridoma Fusion

Monoclonal antibody to epitopes of any of the peptides identified and isolated as described can be prepared from murine hybridomas according to the classical method of Kohler, G. and Milstein, C., Nature 256:495 (1975) or any of the well-known derivative methods thereof. Briefly, a mouse is repetitively inoculated with a few micrograms of the selected protein or peptides derived therefrom

over a period of a few weeks. The mouse is then sacrificed, and the antibody producing cells of the spleen isolated. The spleen cells are fused by means of polyethylene glycol with mouse myeloma cells, and the excess unfused cells destroyed by growth of the system on selective media comprising aminopterin (HAT media). The successfully fused cells are diluted and aliquots of the dilution placed in wells of a microtiter plate where growth of the culture is continued. Antibody-producing clones are identified by detection of antibody in the supernatant fluid of the wells by immunoassay procedures, such as ELISA, as described by Engvall, E., "Enzyme immunoassay ELISA and EMIT," Meth. Enzymol. 70:419 (1980), and derivative methods thereof. Selected positive clones can be expanded and their monoclonal antibody product harvested for use. Detailed procedures for monoclonal antibody production are described in Davis, L. et al. Basic Methods in Molecular Biology Elsevier, New York. Section 21-2.

Polyclonal Antibody Production by Immunization

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Polyclonal antiserum containing antibodies to heterogeneous epitopes of a single protein or a peptide can be prepared by immunizing suitable animals with the expressed protein or peptides derived therefrom described above, which can be unmodified or modified to enhance immunogenicity. Effective polyclonal antibody production is affected by many factors related both to the antigen and the host species. For example, small molecules tend to be less immunogenic than larger molecules and can require the use of carriers and adjuvant. Also, host animals vary in response to site of inoculations and dose, with both inadequate or excessive doses of antigen resulting in low titer antisera. Small doses (ng level) of antigen administered at multiple intradermal sites appears to be most reliable. An effective immunization protocol for rabbits can be found in Vaitukaitis, J. et al. J. Clin. Endocrinol. Metab. 33:988-991 (1971).

Booster injections can be given at regular intervals, and antiserum harvested when antibody titer thereof, as determined semi-quantitatively, for example, by double immunodiffusion in agar against known concentrations of the antigen, begins to fall. See, for example, Ouchterlony, O. et al., Chap. 19 in: **Handbook of Experimental Immunology** D. Wier (ed) Blackwell (1973). Plateau concentration of antibody is usually in the range of 0.1 to 0.2 mg/ml of serum (about 12μM). Affinity of the antisera for the antigen is determined by preparing competitive binding curves, as described, for example, by Fisher, D., Chap. 42 in: **Manual of Clinical Immunology**, 2d Ed. (Rose and Friedman, Eds.) Amer. Soc. For Microbiol., Washington, D.C. (1980).

Antibody preparations prepared according to either protocol are useful in quantitative immunoassays which determine concentrations of antigen-bearing substances in biological samples; they are also used semi-quantitatively or qualitatively to identify the presence of antigen in a biological sample. The antibodies can also be used in therapeutic compositions for killing bacterial cells expressing the protein.

EXAMPLE 8

Screening Chemical Libraries

A. Protein-Based Assays

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Having isolated and expressed bacterial proteins shown to be required for bacterial proliferation, the present invention further contemplates the use of these expressed proteins in assays to screen libraries of compounds for potential drug candidates. The generation of chemical libraries is well known in the art. For example combinatorial chemistry can be used to generate a library of compounds to be screened in the assays described herein. A combinatorial chemical library is a collection of diverse chemical compounds generated by either chemical synthesis or biological synthesis by combining a number of chemical "building blocks" reagents. For example, a linear combinatorial chemical library such as a polypeptide library is formed by combining amino acids in every possible combination to yield peptides of a given length. Millions of chemical compounds theoretically can be synthesized through such combinatorial use of chemical building blocks. For example, one commentator observed that the systematic, combinatorial mixing of 100 interchangeable chemical building blocks results in the theoretical synthesis of 100 million tetrameric compounds or 10 billion pentameric compounds. (Gallop et al., "Applications of Combinatorial Technologies to Drug Discovery, Background and Peptide Combinatorial Libraries," Journal of Medicinal Chemistry, Vol. 37, No. 9, 1233-1250 (1994). Other chemical libraries known to those in the art may also be used, including natural product libraries.

Once generated, combinatorial libraries can be screened for compounds that possess desirable biological properties. For example, compounds which may be useful as drugs or to develop drugs would likely have the ability to bind to the target protein identified, expressed and purified as discussed above. Further, if the identified target protein is an enzyme, candidate compounds would likely interfere with the enzymatic properties of the target protein. Any enzyme can be a target protein. For example, the enzymatic function of a target protein can be to serve as a protease, nuclease, phosphatase, dehydrogenase, transporter protein, transcriptional enzyme, and any other type of enzyme known or unknown. Thus, the present invention contemplates using the protein products described above to screen combinatorial and other chemical libraries.

Those in the art will appreciate that a number of techniques exist for characterizing target proteins in order to identify molecules useful for the discovery and development of therapeutics. For example, some techniques involve the generation and use of small peptides to probe and analyze target proteins both biochemically and genetically in order to identify and develop drug leads. Such techniques include the methods described in PCT publications No. WO9935494, WO9819162, WO9954728.

In another example, the target protein is a serine protease and the substrate of the enzyme is known. The present example is directed towards the analysis of libraries of compounds to identify compounds that function as inhibitors of the target enzyme. First, a library of small molecules is

generated using methods of combinatorial library formation well known in the art. U.S. Patent NOs. 5,463,564 and 5,574, 656, to Agrafiotis, et al., entitled "System and Method of Automatically Generating Chemical Compound with Desired Properties," are two such teachings. Then the library compounds are screened to identify library compounds that possess desired structural and functional properties. U.S. Patent No. 5,684,711, also discusses a method for screening libraries.

To illustrate the screening process, the combined target and chemical compounds of the library are exposed to and permitted to interact with the purified enzyme. A labeled substrate is added to the incubation. The label on the substrate is such that a detectable signal is emitted from metabolized substrate molecules. The emission of this signal permits one to measure the effect of the combinatorial library compounds on the enzymatic activity of target enzymes. The characteristics of each library compound is encoded so that compounds demonstrating activity against the enzyme can be analyzed and features common to the various compounds identified can be isolated and combined into future iterations of libraries.

Once a library of compounds is screened, subsequent libraries are generated using those chemical building blocks that possess the features shown in the first round of screen to have activity against the target enzyme. Using this method, subsequent iterations of candidate compounds will possess more and more of those structural and functional features required to inhibit the function of the target enzyme, until a group of enzyme inhibitors with high specificity for the enzyme can be found. These compounds can then be further tested for their safety and efficacy as antibiotics for use in mammals.

It will be readily appreciated that this particular screening methodology is exemplary only. Other methods are well known to those skilled in the art. For example, a wide variety of screening techniques are known for a large number of naturally-occurring targets when the biochemical function of the target protein is known.

25 B. Cell-based Assays

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Current cell-based assays used to identify or to characterize compounds for drug discovery and development frequently depend on detecting the ability of a test compound to inhibit the activity of a target molecule located within a cell or located on the surface of a cell. An advantage of cell-based assays is that they allow the effect of a compound on a target molecule's activity to be detected within the physiologically relevant environment of the cell as opposed to an *in vitro* environment. Most often such target molecules are proteins such as enzymes, receptors and the like. However, target molecules may also include other molecules such as DNAs, lipids, carbohydrates and RNAs including messenger RNAs, ribosomal RNAs, tRNAs and the like. A number of highly sensitive cell-based assay methods are available to those of skill in the art to detect binding and interaction of test compounds with specific target molecules. However, these methods are generally not highly effective when the test compound binds to or otherwise interacts with its target molecule with moderate or low affinity. In addition, the target molecule may not be

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readily accessible to a test compound in solution, such as when the target molecule is located inside the cell or within a cellular compartment such as the periplasm of a bacterial cell. Thus, current cell-based assay methods are limited in that they are not effective in identifying or characterizing compounds that interact with their targets with moderate to low affinity or compounds that interact with targets that are not readily accessible.

Cell-based assays practiced in the art. These advantages derive from the use of sensitized cells in which the level or activity of a proliferation-required gene product (the target molecule) has been specifically reduced to the point where the presence or absence of its function becomes a rate-determining step for cellular proliferation. Bacterial, fungal, plant, or animal cells can all be used with the present method. Such sensitized cells become much more sensitive to compounds that are active against the affected target molecule. Thus, cell-based assays of the present invention are capable of detecting compounds exhibiting low or moderate potency against the target molecule of interest because such compounds are substantially more potent on sensitized cells than on non-sensitized cells. The affect may be such that a test compound may be two to several times more potent, at least 10 times more potent, at least 20 times more potent, at least 50 times more potent, at least 100 times more potent, at least 100 times more potent, or even more than 1000 times more potent when tested on the sensitized cells as compared to the non-sensitized cells.

Due in part to the increased appearance of antibiotic resistance in pathogenic microorganisms and to the significant side-effects associated with some currently used antibiotics, novel antibiotics acting at new targets are highly sought after in the art. Yet, another limitation in the current art related to cell-based assays is the problem of identifying hits against the same kinds of target molecules in the same limited set of biological pathways over and over again. This may occur when compounds acting at such new targets are discarded, ignored or fail to be detected because compounds acting at the "old" targets are encountered more frequently and are more potent than compounds acting at the new targets. As a result, the majority of antibiotics in use currently interact with a relatively small number of target molecules within an even more limited set of biological pathways.

The use of sensitized cells of the current invention provides a solution to the above problem in two ways. First, desired compounds acting at a target of interest, whether a new target or a previously known but poorly exploited target, can now be detected above the "noise" of compounds acting at the "old" targets due to the specific and substantial increase in potency of such desired compounds when tested on the sensitized cells of the current invention. Second, the methods used to sensitize cells to compounds acting at a target of interest may also sensitize these cells to compounds acting at other target molecules within the same biological pathway. For example, expression of an antisense molecule to a gene encoding a ribosomal protein is expected to sensitize the cell to compounds acting at that ribosomal protein and may also sensitize the cells to

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compounds acting at any of the ribosomal components (proteins or rRNA) or even to compounds acting at any target which is part of the protein synthesis pathway. Thus an important advantage of the present invention is the ability to reveal new targets and pathways that were previously not readily accessible to drug discovery methods.

Sensitized cells of the present invention are prepared by reducing the activity or level of a target molecule. The target molecule may be a gene product, such as an RNA or polypeptide produced from the proliferation-required nucleic acids described herein. Alternatively, the target may be a gene product such as an RNA or polypeptide which is produced from a sequence within the same operon as the proliferation-required nucleic acids described herein. In addition, the target may be an RNA or polypeptide in the same biological pathway as the proliferation-required nucleic acids described herein. Such biological pathways include, but are not limited to, enzymatic, biochemical and metabolic pathways as well as pathways involved in the production of cellular structures such the cell wall.

Current methods employed in the arts of medicinal and combinatorial chemistries are able to make use of structure-activity relationship information derived from testing compounds in various biological assays including direct binding assays and cell-based assays. Occasionally compounds are directly identified in such assays that are sufficiently potent to be developed as drugs. More often, initial hit compounds exhibit moderate or low potency. Once a hit compound is identified with low or moderate potency, directed libraries of compounds are synthesized and tested in order to identify more potent leads. Generally these directed libraries are combinatorial chemical libraries consisting of compounds with structures related to the hit compound but containing systematic variations including additions, subtractions and substitutions of various structural features. When tested for activity against the target molecule, structural features are identified that either alone or in combination with other features enhance or reduce activity. This information is used to design subsequent directed libraries containing compounds with enhanced activity against the target molecule. After one or several iterations of this process, compounds with substantially increased activity against the target molecule are identified and may be further developed as drugs. This process is facilitated by use of the sensitized cells of the present invention since compounds acting at the selected targets exhibit increased potency in such cell-based assays, thus; more compounds can now be characterized providing more useful information than would be obtained otherwise.

Thus, it is now possible using cell-based assays of the present invention to identify or characterize compounds that previously would not have been readily identified or characterized including compounds that act at targets that previously were not readily exploited using cell-based assays. The process of evolving potent drug leads from initial hit compounds is also substantially improved by the cell-based assays of the present invention because, for the same number of test compounds, more structure-function relationship information is likely to be revealed.

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The method of sensitizing a cell entails selecting a suitable gene or operon. A suitable gene or operon is one whose expression is required for the proliferation of the cell to be sensitized. The next step is to introduce into the cells to be sensitized, an antisense RNA capable of hybridizing to the suitable gene or operon or to the RNA encoded by the suitable gene or operon. Introduction of the antisense RNA can be in the form of an expression vector in which antisense RNA is produced under the control of an inducible promoter. The amount of antisense RNA produced is limited by varying the inducer concentration to which the cell is exposed and thereby varying the activity of the promoter driving transcription of the antisense RNA. Thus, cells are sensitized by exposing them to an inducer concentration that results in a sub-lethal level of antisense RNA expression.

In one embodiment of the cell-based assays, the identified exogenous E. coli nucleotide sequences of the present invention are used to inhibit the production of a proliferation-required protein. Expression vectors producing antisense RNA complementary to identified genes required for proliferation are used to limit the concentration of a proliferation-required protein without severely inhibiting growth. To achieve that goal, a growth inhibition dose curve of inducer is calculated by plotting various doses of inducer against the corresponding growth inhibition caused by the antisense expression. From this curve, various percentages of antisense induced growth inhibition, from 1 to 100% can be determined. If the promoter contained in the expression vector contains a lac operator the transcription is regulated by lac repressor and expression from the promoer is inducible with IPTG. For example, the highest concentration of the inducer IPTG that does not reduce the growth rate significantly (0% growth inhibition) can be predicted from the curve. Cellular proliferation can be monitored by growth medium turbidity via OD measurements. In another example, the concentration of inducer that reduces growth by 25% can be predicted from the curve. In still another example, a concentration of inducer that reduces growth by 50% can be calculated. Additional parameters such as colony forming units (cfu) can be used to measure cellular viability.

Cells to be assayed are exposed to the above-determined concentrations of inducer. The presence of the inducer at this sub-lethal concentration reduces the amount of the proliferation required gene product to a low amount in the cell that will limit but not prevent growth. Cells grown in the presence of this concentration of inducer are therefore specifically more sensitive to inhibitors of the proliferation-required protein or RNA of interest or to inhibitors of proteins or RNAs in the same biological pathway as the proliferation-required protein or RNA of interest but not to inhibitors of unrelated proteins or RNAs.

Cells pretreated with sub-inhibitory concentrations of inducer and thus containing a reduced amount of proliferation-required target gene product are then used to screen for compounds that reduce cell growth. The sub-lethal concentration of inducer may be any concentration consistent with the intended use of the assay to identify candidate compounds to which the cells are more sensitive. For example, the sub-lethal concentration of the inducer may be such that growth

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inhibition is at least about 5%, at least about 8%, at least about 10%, at least about 20%, at least about 30%, at least about 40%, at least about 50%, at least about 60% at least about 75%, 90%, 95% or more. Cells which are pre-sensitized using the preceding method are more sensitive to inhibitors of the target protein because these cells contain less target protein to be inhibited than do wild-type cells.

In another embodiment of the cell-based assays of the present invention, the level or activity of a proliferation required gene product is reduced using a mutation, such as a temperature sensitive mutation, in the proliferation-required sequence and an antisense nucleic acid complementary to the proliferation-required sequence. Growing the cells at an intermediate temperature between the permissive and restrictive temperatures of the temperature sensitive mutant where the mutation is in a proliferation-required gene produces cells with reduced activity of the proliferation-required gene product. The antisense RNA complementary to the proliferationrequired sequence further reduces the activity of the proliferation required gene product. Drugs that may not have been found using either the temperature sensitive mutation or the antisense nucleic acid alone may be identified by determining whether cells in which expression of the antisense nucleic acid has been induced and which are grown at a temperature between the permissive temperature and the restrictive temperature are substantially more sensitive to a test compound than cells in which expression of the antisense nucleic acid has not been induced and which are grown at a permissive temperature. Also drugs found previously from either the antisense nucleic acid alone or the temperature sensitive mutation alone may have a different sensitivity profile when used in cells combining the two approaches, and that sensitivity profile may indicate a more specific action of the drug in inhibiting one or more activities of the gene product.

Temperature sensitive mutations may be located at different sites within the gene and correspond to different domains of the protein. For example, the *dnaB* gene of *Escherichia coli* encodes the replication fork DNA helicase. DnaB has several domains, including domains for oligomerization, ATP hydrolysis, DNA binding, interaction with primase, interaction with DnaC, and interaction with DnaA [(Biswas, E.E. and Biswas, S.B. 1999 Mechanism and DnaB helicase of *Escherichia coli*: structural domains involved in ATP hydrolysis, DNA binding, and oligomerization. Biochem. 38:10919-10928; Hiasa, H. and Marians, K.J. 1999 Initiation of bidirectional replication at the chromosomal origin is directed by the interaction between helicase and primase. J. Biol. Chem. 274:27244-27248; San Martin, C., Radermacher, M., Wolpensinger, B., Engel, A., Miles, C.S., Dixon, N.E., and Carazo, J.M. 1998 Three-dimensional reconstructions from cryoelectron microscopy images reveal an intimate complex between helicase DnaB and its loading partner DnaC. Structure 6:501-9; Sutton, M.D., Carr, K.M., Vicente, M., and Kaguni, J.M. 1998 *Escherichia coli* DnaA protein. The N-terminal domain and loading of DnaB helicase at the *E. coli* chromosomal. J. Biol. Chem. 273:34255-62)]. Temperature sensitive mutations in different domains of DnaB confer different phenotypes at the restrictive temperature, which include either an

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abrupt stop or slow stop in DNA replication with or without DNA breakdown (Wechsler, J.A. and Gross, J.D. 1971. *Escherichia coli* mutants temperature-sensitive for DNA synthesis. Mol. Gen. Genetics 113:273-284) and termination of growth or cell death. Combining the use of temperature sensitive mutations in the *dnaB* gene that cause cell death at the restrictive temperature with an antisense to the *dnaB* gene could lead to the discovery of very specific and effective inhibitors of one or a subset of activities exhibited by DnaB.

It will be appreciated that the above method may be performed with any mutation which reduces but does not eliminate the activity or level of the gene product which is required for proliferation.

When screening for antimicrobial agents against a gene product required for proliferation, growth inhibition of cells containing a limiting amount of that proliferation-required gene product can be assayed. Growth inhibition can be measured by directly comparing the amount of growth, measured by the optical density of the growth medium, between an experimental sample and a control sample. Alternative methods for assaying cell proliferation include measuring green fluorescent protein (GFP) reporter construct emissions, various enzymatic activity assays, and other methods well known in the art.

It will be appreciated that the above method may be performed in solid phase, liquid phase or a combination of the two. For example, cells grown on nutrient agar containing the inducer of the antisense construct may be exposed to compounds spotted onto the agar surface. A compound's effect may be judged from the diameter of the resulting killing zone, the area around the compound application point in which cells do not grow. Multiple compounds may be transferred to agar plates and simultaneously tested using automated and semi-automated equipment including but not restricted to multi-channel pipettes (for example the Beckman Multimek) and multi-channel spotters (for example the Genomic Solutions Flexys). In this way multiple plates and thousands to millions of compounds may be tested per day.

The compounds may also be tested entirely in liquid phase using microtiter plates as described below. Liquid phase screening may be performed in microtiter plates containing 96, 384, 1536 or more wells per microtiter plate to screen multiple plates and thousands to millions of compounds per day. Automated and semi-automated equipment may be used for addition of reagents (for example cells and compounds) and determination of cell density.

EXAMPLE 9

Cell-based Assay Using Antisense Complementary to Genes Encoding Ribosomal Proteins

The effectiveness of the above cell-based assay was validated using constructs expressing antisense RNA to the proliferation required E. coli genes rplL, rplJ, and rplW encoding ribosomal proteins L7/L12, L10 and L23 respectively. These proteins are part of the protein synthesis apparatus of the cell and as such are required for proliferation. These constructs were used to test the effect of antisense expression on cell sensitivity to antibiotics known to bind to the ribosome

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and thereby inhibit protein synthesis. Constructs expressing antisense RNA to several other genes (elaD, visC, yohH, and atpE/B), the products of which are not involved in protein synthesis were used for comparison.

First, pLEX5BA (Krause et al., J. Mol. Biol. 274: 365 (1997)) expression vectors containing antisense constructs to either rplW or to elaD were introduced into separate E. coli cell populations. Vector introduction is a technique well known to those of ordinary skill in the art. The expression vectors of this example contain IPTG inducible promoters that drive the expression of the antisense RNA in the presence of the inducer. However, those skilled in the art will appreciate that other inducible promoters may also be used. Suitable expression vectors are also well known in the art. The E. coli antisense clones to genes encoding ribosomal proteins L7/L12, L10 and L23 were used to test the effect of antisense expression on cell sensitivity to the antibiotics known to bind to these proteins. Expression vectors containing antisense to either the genes encoding L7/L12 and L10 or L23 were introduced into separate E. coli cell populations.

The cell populations were exposed to a range of IPTG concentrations in liquid medium to obtain the growth inhibitory dose curve for each clone (Fig. 1). First, seed cultures were grown to a particular turbidity that is measured by the optical density (OD) of the growth solution. The OD of the solution is directly related to the number of bacterial cells contained therein. Subsequently, sixteen 200 ul liquid medium cultures were grown in a 96 well microtiter plate at 37° C with a range of IPTG concentrations in duplicate two-fold serial dilutions from 1600 uM to 12.5 uM (final concentration). Additionally, control cells were grown in duplicate without IPTG. These cultures were started from equal amounts of cells derived from the same initial seed culture of a clone of interest. The cells were grown for up to 15 hours and the extent of growth was determined by measuring the optical density of the cultures at 600 nm. When the control culture reached mid-log phase the percent growth (relative to the control culture) for each of the IPTG containing cultures was plotted against the log concentrations of IPTG to produce a growth inhibitory dose response curve for the IPTG. The concentration of IPTG that inhibits cell growth to 50% (IC₅₀) as compared to the 0 mM IPTG control (0% growth inhibition) was then calculated from the curve. Under these conditions, an amount of antisense RNA was produced that reduced the expression levels of rplW and elaD to a degree such that growth was inhibited by 50%.

Alternative methods of measuring growth are also contemplated. Examples of these methods include measurements of proteins, the expression of which is engineered into the cells being tested and can readily be measured. Examples of such proteins include green fluorescent protein (GFP) and various enzymes.

Cells were pretreated with the selected concentration of IPTG and then used to test the sensitivity of cell populations to tetracycline, erythromycin and other protein synthesis inhibitors. Figure 2 is an IPTG dose response curve in *E. coli* transformed with an IPTG-inducible plasmid containing either an antisense clone to the *E. coli* rplW gene (AS-rplW) which encodes ribosomal

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protein L23 which is required for protein synthesis and essential for cell proliferation, or an antisense clone to the *elaD* (AS-*elaD*) gene which is not known to be involved in protein synthesis and which is also essential for proliferation.

An example of a tetracycline dose response curve is shown in Figures 2A and 2B for the rplW and elaD genes, respectively. Cells were grown to log phase and then diluted into media alone or media containing IPTG at concentrations which give 20% and 50% growth inhibition as determined by IPTG dose response curves. After 2.5 hours, the cells were diluted to a final OD₆₀₀ of 0.002 into 96 well plates containing (1) +/- IPTG at the same concentrations used for the 2.5 hour pre-incubation; and (2) serial two-fold dilutions of tetracycline such that the final concentrations of tetracycline range from 1 µg/ml to 15.6 ng/ml and 0 µg/ml. The 96 well plates were incubated at 37°C and the OD600 was read by a plate reader every 5 minutes for up to 15 hours. For each IPTG concentration and the no IPTG control, tetracycline dose response curves were determined when the control (absence of tetracycline) reached 0.1 OD₆₀₀. To compare tetracycline sensitivity with and without IPTG, tetracycline IC_{50s} were determined from the dose response curves (Figs. 3A-B). Cells with reduced levels of L23 (AS-rplW) showed increased sensitivity to tetracycline (Fig. 2A) as compared to cells with reduced levels of the elaD gene product (AS-elaD) (Fig. 2B). Figure 3 shows a summary bar chart in which the ratios of tetracycline IC50s determined in the presence of IPTG which gives 50% growth inhibition versus tetracycline IC_{50s} determined without IPTG (fold increase in tetracycline sensitivity) were plotted. Cells with reduced levels of either L7/L12 (encoded by genes rplL, rplJ) or L23 (encoded by the rplW gene) showed increased sensitivity to tetracycline (Fig. 3). Cells expressing antisense to genes not known to be involved in protein synthesis (AS-atpB/E, AS-visC, AS-elaD, AS-yohH) did not show the same increased sensitivity to tetracycline, validating the specificity of this assay (Fig. 3).

In addition to the above, it has been observed in initial experiments that clones expressing antisense RNA to genes involved in protein synthesis (including genes encoding ribosomal proteins L7/L12 & L10, L7/L12 alone, L22, and L18, as well as genes encoding rRNA and Elongation Factor G) have increased sensitivity to the macrolide, erythromycin, whereas clones expressing antisense to the non-protein synthesis genes elaD, atpB/E and visC do not. Furthermore, the clone expressing antisense to rplL and rplJ does not show increased sensitivity to nalidixic acid and ofloxacin, antibiotics which do not inhibit protein synthesis.

The results with the ribosomal protein genes rplL, rplJ, and rplW as well as the initial results using various other antisense clones and antibiotics show that limiting the concentration of an antibiotic target makes cells more sensitive to the antimicrobial agents that specifically interact with that protein. The results also show that these cells are sensitized to antimicrobial agents that inhibit the overall function in which the protein target is involved but are not sensitized to antimicrobial agents that inhibit other functions.

The cell-based assay described above may also be used to identify the biological pathway in which a proliferation-required nucleic acid or its gene product lies. In such methods, cells expressing a sub-lethal level of antisense to a target proliferation-required nucleic acid and control cells in which expression of the antisense has not been induced are contacted with a panel of antibiotics known to act in various pathways. If the antibiotic acts in the pathway in which the target proliferation-required nucleic acid or its gene product lies, cells in which expression of the antisense has been induced will be more sensitive to the antibiotic than cells in which expression of the antisense has not been induced.

As a control, the results of the assay may be confirmed by contacting a panel of cells expressing antisense nucleic acids to many different proliferation-required genes including the target proliferation-required gene. If the antibiotic is acting specifically, heightened sensitivity to the antibiotic will be observed only in the cells expressing antisense to a target proliferation-required gene (or cells expressing antisense to other proliferation-required genes in the same pathway as the target proliferation-required gene) but will not be observed generally in all cells expressing antisense to proliferation-required genes.

Similarly, the above method may be used to determine the pathway on which a test compound, such as a test antibiotic acts. A panel of cells, each of which expresses antisense to a proliferation-required nucleic acid in a known pathway, is contacted with a compound for which it is desired to determine the pathway on which it acts. The sensitivity of the panel of cells to the test compound is determined in cells in which expression of the antisense has been induced and in control cells in which expression of the antisense has not been induced. If the test compound acts on the pathway on which an antisense nucleic acid acts, cells in which expression of the antisense has been induced will be more sensitive to the compound than cells in which expression of the antisense has not been induced. In addition, control cells in which expression of antisense to proliferation-required genes in other pathways has been induced will not exhibit heightened sensitivity to the compound. In this way, the pathway on which the test compound acts may be determined.

The Example below provides one method for performing such assays.

EXAMPLE 10

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Identification of the Pathway in which a Proliferation-Required

Gene Lies or the Pathway on which an Antibiotic Acts

A. Preparation of Bacterial Stocks for Assay

To provide a consistent source of cells to screen, frozen stocks of host bacteria containing the desired antisense construct are prepared using standard microbiological techniques. For example, a single clone of the organism can be isolated by streaking out a sample of the original stock onto an agar plate containing nutrients for cell growth and an antibiotic for which the antisense construct contains a gene which confers resistance. After overnight growth an isolated

colony is picked from the plate with a sterile needle and transferred to an appropriate liquid growth media containing the antibiotic required for maintenance of the plasmid. The cells are incubated at 30°C to 37°C with vigorous shaking for 4 to 6 hours to yield a culture in exponential growth. Sterile glycerol is added to 15% (volume to volume) and 100µL to 500 µL aliquots are distributed into sterile cryotubes, snap frozen in liquid nitrogen, and stored at -80°C for future assays.

B. Growth of Bacteria for Use in the Assay

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A day prior to an assay, a stock vial is removed from the freezer, rapidly thawed (37°C water bath) and a loop of culture is streaked out on an agar plate containing nutrients for cell growth and an antibiotic to which the antisense construct confers resistance. After overnight growth at 37°C, ten randomly chosen, isolated colonies are transferred from the plate (sterile inoculum loop) to a sterile tube containing 5 mL of LB medium containing the antibiotic to which the antisense vector confers resistance. After vigorous mixing to form a homogeneous cell suspension, the optical density of the suspension is measured at 600 nm (OD₆₀₀) and if necessary an aliquot of the suspension is diluted into a second tube of 5 mL, sterile, LB medium plus antibiotic to achieve an OD₆₀₀ \leq 0.02 absorbance units. The culture is then incubated at 37° C for 1-2 hrs with shaking until the OD₆₀₀ reaches OD 0.2 – 0.3. At this point the cells are ready to be used in the assay.

C. Selection of Media to be Used in Assay

Two fold dilution series of the inducer are generated in culture media containing the appropriate antibiotic for maintenance of the antisense construct. Several media are tested side by side and three to four wells are used to evaluate the effects of the inducer at each concentration in each media. For example, M9 minimal media, LB broth, TBD broth and Muller-Hinton media may be tested with the inducer IPTG at the following concentrations, 50 μM, 100 μM, 200 μM, 400 μM, 600 μM, 800 μM and 1000 μM. Equal volumes of test media-inducer and cells are added to the wells of a 384 well microtiter plate and mixed. The cells are prepared as described above and diluted 1:100 in the appropriate media containing the test antibiotic immediately prior to addition to the microtiter plate wells. For a control, cells are also added to several wells of each media that do not contain inducer, for example 0 μM IPTG. Cell growth is monitored continuously by incubation at 37°C in a microtiter plate reader monitoring the OD₆₀₀ of the wells over an 18-hour period. The percent inhibition of growth produced by each concentration of inducer is calculated by comparing the rates of logarithmic growth against that exhibited by cells growing in media without inducer. The medium yielding greatest sensitivity to inducer is selected for use in the assays described below.

D. Measurement of Test Antibiotic Sensitivity in the Absence of Antisense Construct Induction

Two-fold dilution series of antibiotics with a known mechanism of action are generated in the culture media selected for further assay development that has been supplemented with the antibiotic used to maintain the construct. A panel of test antibiotics known to act on different

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pathways is tested side by side with three to four wells being used to evaluate the effect of a test antibiotic on cell growth at each concentration. Equal volumes of test antibiotic and cells are added to the wells of a 384 well microtiter plate and mixed. Cells are prepared as described above using the media selected for assay development supplemented with the antibiotic required to maintain the antisense construct and are diluted 1:100 in identical media immediately prior to addition to the microtiter plate wells. For a control, cells are also added to several wells that contain the solvent used to dissolve the antibiotics but no antibiotic. Cell growth is monitored continuously by incubation at 37°C in a microtiter plate reader monitoring the OD₆₀₀ of the wells over an 18-hour period. The percent inhibition of growth produced by each concentration of antibiotic is calculated by comparing the rates of logarithmic growth against that exhibited by cells growing in media without antibiotic. A plot of percent inhibition against log[antibiotic concentration] allows extrapolation of an IC₅₀ value for each antibiotic.

E. Measurement of Test Antibiotic Sensitivity in the Presence of Antisense Construct Inducer

The culture media selected for use in the assay is supplemented with inducer at concentrations shown to inhibit cell growth by 50% and 80% as described above and the antibiotic used to maintain the construct. Two fold dilution series of the panel of test antibiotics used above are generated in each of these media. Several antibiotics are tested side by side with three to four wells being used to evaluate the effects of an antibiotic on cell growth at each concentration, in each media. Equal volumes of test antibiotic and cells are added to the wells of a 384 well microtiter. plate and mixed. Cells are prepared as described above using the media selected for use in the assay supplemented with the antibiotic required to maintain the antisense construct. The cells are diluted 1:100 into two 50 mL aliquots of identical media containing concentrations of inducer that have been shown to inhibit cell growth by 50% and 80 % respectively and incubated at 37°C with shaking for 2.5 hours. Immediately prior to addition to the microtiter plate wells, the cultures are adjusted to an appropriate OD₆₀₀ (typically 0.002) by dilution into warm (37°C) sterile media supplemented with identical concentrations of the inducer and antibiotic used to maintain the antisense construct. For a control, cells are also added to several wells that contain solvent used to dissolve test antibiotics but which contain no antibiotic. Cell growth is monitored continuously by incubation at 37°C in a microtiter plate reader monitoring the OD600 of the wells over an 18-hour period. The percent inhibition of growth produced by each concentration of antibiotic is calculated by comparing the rates of logarithmic growth against that exhibited by cells growing in media without antibiotic. A plot of percent inhibition against log[antibiotic concentration] allows extrapolation of an IC₅₀ value for each antibiotic.

F. Determining the Specificity of the Test Antibiotics

A comparison of the IC₅₀s generated by antibiotics of known mechanism of action under antisense induced and non-induced conditions allows the pathway in which a proliferation-required

nucleic acid lies to be identified. If cells expressing an antisense nucleic acid against a proliferation-required gene are selectively sensitive to an antibiotic acting via a particular pathway, then the gene against which the antisense acts is involved in the pathway in which the antibiotic acts.

G. Identification of Pathway in which a Test Antibiotic Acts

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As discussed above, the cell-based assay may also be used to determine the pathway against which a test antibiotic acts. In such an analysis, the pathways against which each member of a panel of antisense nucleic acids acts are identified as described above. A panel of cells, each containing an inducible nucleic acid complementary to a gene in a known proliferation-required pathway, is contacted with a test antibiotic for which it is desired to determine the pathway on which it acts under inducing an non-inducing conditions. If heightened sensitivity is observed in induced cells expressing antisense complementary to a gene in a particular pathway but not in induced cells expressing antisense complementary to genes in other pathways, then the test antibiotic acts against the pathway for which heightened sensitivity was observed.

One skilled in the art will appreciate that further optimization of the assay conditions, such as the concentration of inducer used to induce antisense expression and/or the growth conditions used for the assay (for example incubation temperature and media components) may further increase the selectivity and/or magnitude of the antibiotic sensitization exhibited.

The following example confirms the effectiveness of the methods described above.

EXAMPLE 11

Identification of the Pathway in which a Proliferation-Required Gene Lies

Antibiotics of various chemical classes and modes of action were purchased from Sigma Chemicals (St. Louis, MO). Stock solutions were prepared by dissolving each antibiotic in an appropriate aqueous solution based on information provided by the manufacturer. The final working solution of each antibiotic contained no more than 0.2% (w/v) of any organic solvent. To determine their potency against a bacterial strain engineered for expression of an antisense complementary to a proliferation-required gene encoding 50S ribosomal protein, each antibiotic was serially diluted two or three fold in growth medium supplemented with the appropriate antibiotic for maintenance of the anti-sense construct. At least ten dilutions were prepared for each antibiotic. 25 µL aliquots of each dilution were transferred to discrete wells of a 384-well microplate (the assay plate) using a multi-channel pipette. Quadruplicate wells were used for each dilution of an antibiotic under each treatment condition (plus and minus inducer). Each assay plate contained twenty wells for cell growth controls (growth media replacing antibiotic), ten wells for each treatment (plus and minus inducer, in this example IPTG). Assay plates were usually divided into the two treatments: half the plate containing induced cells and an appropriate concentrations of inducer (in this example IPTG) to maintain the state of induction, the other half containing noninduced cells in the absence of IPTG.

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Cells for the assay were prepared as follows. Bacterial cells containing a construct, from which expression of antisense nucleic acid complementary to rplL and rplJ, which encode proliferation-required 50S ribosomal subunit proteins, is inducible in the presence of IPTG, were grown into exponential growth (OD600 0.2 to 0.3) and then diluted 1:100 into fresh media containing either 400 µM or 0 µM inducer (IPTG). These cultures were incubated at 37° C for 2.5 hr. After a 2.5 hr incubation, induced and non-induced cells were respectively diluted into an assay medium at a final OD₆₀₀ value of 0.0004. The medium contained an appropriate concentration of the antibiotic for the maintenance of the anti-sense construct. In addition, the medium used to dilute induced cells was supplemented with 800 µM IPTG so that addition to the assay plate would result in a final IPTG concentration of 400 μM . Induced and non-induced cell suspensions were dispensed (25 µl/well) into the appropriate wells of the assay plate as discussed previously. The plate was then loaded into a plate reader, incubated at constant temperature, and cell growth was monitored in each well by the measurement of light scattering at 595 nm. Growth was monitored every 5 minutes until the cell culture attained a stationary growth phase. For each concentration of antibiotic, a percentage inhibition of growth was calculated at the time point corresponding to midexponential growth for the associated control wells (no antibiotic, plus or minus IPTG). For each antibiotic and condition (plus or minus IPTG), a plot of percent inhibition versus log of antibiotic concentration was generated and the IC50 determined. A comparison of the IC50 for each antibiotic in the presence and absence of IPTG revealed whether induction of the antisense construct sensitized the cell to the mechanism of action exhibited by the antibiotic. Cells which exhibited a significant (standard statistical analysis) numerical decrease in the IC₅₀ value in the presence of inducer were considered to have an increased sensitivity to the test antibiotic.

The results are provided in the table below, which lists the classes and names of the antibiotics used in the analysis, the targets of the antibiotics, the IC₅₀ in the absence of IPTG, the IC₅₀ in the presence of IPTG, the concentration units for the IC₅₀s, the fold increase in IC₅₀ in the presence of IPTG, and whether increased sensitivity was observed in the presence of IPTG.

TABLE IV

Effect of Expression of Antisense RNA to rplL and rplJ on Antibiotic Sensitivity

					Fold	
		ICS0	ICS0		Increase in	Sensitivity
ANTIBIOTIC CLASS /Names	TARGET	(-IPTG)	(+IPTG)	Conc. Unit	Sensitivity	Increased?
PROTEIN SYNTHESIS INHIBITOR						,
ANTIBIOTICS						
AMINOGLYCOSIDES						
Gentamicin	30S ribosome function	2715	19.19	ng/ml	141	Yes
Streptomycin	30S ribosome function	11280	191	ng/ml	70	Yes
Spectinomycin	30S ribosome function	18050	<156	lm/gu		Yes
Tobramycin	30S ribosome function	3594	70.58	ng/ml	51	Yes
MACROLIDES	,		i			
Erythromycin	50S ribosome function	7467	187	ng/ml	40	Yes
AROMATIC POYKETIDES						
Tetracycline	30S ribosome function	199.7	1.83	lm/gu	109	Yes
Minocycline	30S ribosome function	668.4	3.897	ng/ml	172	Yes
Doxycycline	30S ribosome function	413.1	27.81	nig/ml	15	Yes
OTHER PROTEIN SYNTHESIS INHIBITORS						
Fusidic acid	Elongation Factor G function	29990	641	ng/ml	94	Yes
Chloramphenicol	30S ribosome function	465.4	1.516	ng/ml	307	Yes
Lincomycin	50S ribosome function	47150	324.2	ng/ml	145	Yes

		ICS0	IC50		Fold Increase in	Sensitivity
ANTIBIOTIC CLASS /Names	TARGET	(-IPTG)		Conc. Unit Sensitivity	Sensitivity	Increased?
OTHER ANTIBIOTIC MECHANISMS						
B-LACTAMS						
Cefoxitin	Cell wall biosynthesis	2782	2484	ng/ml	~	No
Cefotaxime	Cell wall biosynthesis	24.3	24.16	lm/gu		No
DNA SYNTHESIS INHIBITORS				!		
Nalidixic acid	DNA Gyrase activity	6973	6025	ng/ml	1	No
Ofloxacin	DNA Gyrase activity	49.61	45.89	ng/ml		No
OTHER					•	
Bacitracin	Cell membrane function	4077	4677	mg/ml		No
	Dihydrofolate Reductase					
Trimethoprim	activity	128.9	181.97	ng/ml	-	%
Vancomycin	Cell wall biosynthesis	145400	72550	ng/ml	7	No

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The above results demonstrate that induction of an antisense RNA to genes encoding 50S ribosomal subunit proteins results in a selective and highly significant sensitization of cells to antibiotics that inhibit ribosomal function and protein synthesis. The above results further demonstrate that induction of an antisense construct to an essential gene sensitizes an organism to compounds that interfere with that gene products' biological role. This sensitization is restricted to compounds that interfere with pathways associated with the targeted gene and it's product.

Assays utilizing antisense constructs to essential genes can be used to identify compounds that specifically interfere with the activity of multiple targets in a pathway. Such constructs can be used to simultaneously screen a sample against multiple targets in one pathway in one reaction (Combinatorial HTS).

Furthermore, as discussed above, panels of antisense construct containing cells may be used to characterize the point of intervention of any compound affecting an essential biological pathway including antibiotics with no known mechanism of action.

Another embodiment of the present invention is a method for determining the pathway against which a test antibiotic compound is active in which the activity of target proteins or nucleic acids involved in proliferation-required pathways is reduced by contacting cells with a sub-lethal concentration of a known antibiotic which acts against the target protein or nucleic acid. In one embodiment, the target protein or nucleic acid is a target protein or nucleic acid corresponding to a proliferation-required nucleic acid identified using the methods described above. The method is similar to those described above for determining which pathway a test antibiotic acts against except that rather than reducing the activity or level of a proliferation-required gene product using a sub-lethal level of antisense to a proliferation-required nucleic acid, the activity or level of the proliferation-required gene product is reduced using sub-lethal level of a known antibiotic which acts against the proliferation required gene product.

Interactions between drugs which affect the same biological pathway has been described in the literature. For example, Mecillinam (Amdinocillin) binds to and inactivates the penicillin binding protein 2 (PBP2, product of the *mrdA* in *E. coli*). This antibiotic inteacts with other antibiotics that inhibit PBP2 as well as antibiotics that inhibit other penicillin binding proteins such as PBP3 [(Gutmann, L., Vincent, S., Billot-Klein, D., Acar, J.F., Mrena, E., and Williamson, R. (1986) Involvement of penicillin-binding protein 2 with other penicillin-binding proteins in lysis of *Escherichia coli* by some beta-lactam antibiotics alone and in synergistic lytic effect of amdinocillin (mecillinam). Antimicrobial Agents & Chemotherapy, 30:906-912)]. Interactions between drugs could, therefore, involve two drugs that inhibit the same target protein or nucleic acid or inhibit different proteins or nucleic acids in the same pathway [(Fukuoka, T., Domon, H., Kakuta, M., Ishii, C., Hirasawa, A., Utsui, Y., Ohya, S., and Yasuda, H. (1997) Combination effect between panipenem and vancomycin on highly methicillin-resistant Staphylococcus aureus. Japan. J. Antibio. 50:411-419; Smith, C.E., Foleno, B.E., Barrett, J.F., and Frosc, M.B. (1997) Assessment

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of the synergistic interactions of levofloxacin and ampicillin against *Enterococcus faecium* by the checkerboard agar dilution and time-kill methods. Diagnos. Microbiol. Infect. Disease 27:85-92; den Hollander, J.G., Horrevorts, A.M., van Goor, M.L., Verbrugh, H.A., and Mouton, J.W. (1997) Synergism between tobramycin and ceftazidime against a resistant Pseudomonas aeruginosa strain, tested in an in vitro pharmacokinetic model. Antimicrobial Agents & Chemotherapy. 41:95-110)].

Two drugs may interact even though they inhibit different targets. For example, the proton pump inhibitor, Omeprazole, and the antibiotic, Amoxycillin, two synergistic compounds acting together, can cure *Helicobacter pylori* infection [(Gabryelewicz, A., Laszewicz, W., Dzieniszewski, J., Ciok, J., Marlicz, K., Bielecki, D., Popiela, T., Legutko, J., Knapik, Z., Poniewierka, E. (1997) Multicenter evaluation of dual-therapy (omeprazol and amoxycillin) for *Helicobacter pylori*-associated duodenal and gastric ulcer (two years of the observation). J. Physiol. Pharmacol. 48 Suppl 4:93-105)].

The growth inhibition from the sub-lethal concentration of the known antibiotic may be at least about 5%, at least about 8%, at least about 10%, at least about 20%, at least about 30%, at least about 40%, at least about 50%, at least about 60%, or at least about 75%, or more.

Alternatively, the sub-lethal concentration of the known antibiotic may be determined by measuring the activity of the target proliferation-required gene product rather than by measuring growth inhibition.

Cells are contacted with a combination of each member of a panel of known antibiotics at a sub-lethal level and varying concentrations of the test antibiotic. As a control, the cells are contacted with varying concentrations of the test antibiotic alone. The IC₅₀ of the test antibiotic in the presence and absence of the known antibiotic is determined. If the IC₅₀s in the presence and absence of the known drug are substantially similar, then the test drug and the known drug act on different pathways. If the IC₅₀s are substantially different, then the test drug and the known drug act on the same pathway.

Another embodiment of the present invention is a method for identifying a candidate compound for use as an antibiotic in which the activity of target proteins or nucleic acids involved in proliferation-required pathways is reduced by contacting cells with a sub-lethal concentration of a known antibiotic which acts against the target protein or nucleic acid. In one embodiment, the target protein or nucleic acid is a target protein or nucleic acid corresponding to a proliferation-required nucleic acid identified using the methods described above. The method is similar to those described above for identifying candidate compounds for use as antibiotics except that rather than reducing the activity or level of a proliferation-required gene product using a sub-lethal level of antisense to a proliferation-required nucleic acid, the activity or level of the proliferation-required gene product is reduced using a sub-lethal level of a known antibiotic which acts against the proliferation required gene product.

The growth inhibition from the sub-lethal concentration of the known antibiotic may be at least about 5%, at least about 8%, at least about 10%, at least about 20%, at least about 30%, at least about 40%, at least about 50%, at least about 60%, or at least about 75%, or more.

Alternatively, the sub-lethal concentration of the known antibiotic may be determined by measuring the activity of the target proliferation-required gene product rather than by measuring growth inhibition.

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In order to characterize test compounds of interest, cells are contacted with a panel of known antibiotics at a sub-lethal level and one or more concentrations of the test compound. As a control, the cells are contacted with the same concentrations of the test compound alone. The IC₅₀ of the test compound in the presence and absence of the known antibiotic is determined. If the IC₅₀ of the test compound is substantially different in the presence and absence of the known drug then the test compound is a good candidate for use as an antibiotic. As discussed above, once a candidate compound is identified using the above methods its structure may be optimized using standard techniques such as combinatorial chemistry.

Representative known antibiotics which may be used in each of the above methods are provided in the table below. However, it will be appreciated that other antibiotics may also be used.

ANTIBIOTIC	INHIBITS/TARGET	RESISTANT MUTANTS
Inhibitors of Transcription		:
Rifamycin, 1959 Rifampicin Rifabutin Rifaximin	Inhibits initiation of transcription/\(\beta\)-subunit RNA polymerase, \(rpoB\)	rpoB, crp, cyaA
Streptolydigin	Accelerates transcription chain termination/ß-subunit RNA polymerase	rpoB
Streptovaricin	an acyclic ansamycin, inhibits RNA polymerase	rpoB
Actinomycin D+EDTA	Intercalates between 2 successive G-C pairs, rpoB, inhibits RNA synthesis	pldA
Inhibitors of Nucleic Acid M	etabolism	
Quinolones, 1962 Nalidixic acid Oxolinic acid	α subunit gyrase and/or topoisomerase IV, gyrA	gyrAorB, icd, sloB
Fluoroquinolones Ciprofloxacin, 1983 Norfloxacin	α subunit gyrase, gyrA and/or topoisomerase IV (probable target in Staph)	gyrA norA (efflux in Staph) hipQ
Coumerins Novobiocin	Inhibits ATPase activity of β -subunit gyrase, $gyrB$	gyrB, cysB, cysE, nov, ompA
Coumermycin	Inhibits ATPase activity of β-subunit gyrase, gyrB	gyrB, hisW
Albicidin	DNA synthesis	tsx (nucleoside channel)
Metronidazole	Causes single-strand breaks in DNA	nar

Inhibitors of Metabolic Pathways Sulfonamides, 1932 blocks synthesis of dihydrofolate, dihydrofolP, gpt, pabA, pabB, Sulfanilamide pteroate synthesis, folP pabCTrimethoprim, 1962 Inhibits dihydrofolate reductase, folA folA, thyA Showdomycin ' Nucleoside analogue capable of alkylating nupC, pnp sulfhydryl groups, inhibitor of thymidylate synthetase Thiolactomycin type II fatty acid synthase inhibitor emrBfadB, emrB due to gene dosage **Psicofuranine** Adenosine glycoside antibiotic, target is guaA,B GMP synthetase fabl (envM) Triclosan Inhibits fatty acid synthesis Diazoborines heterocyclic, contains boron, inhibit fatty fabI (envM) Isoniazid acid synthesis, enoyl-ACP reductase, fabl Ethionamide Inhibitors of Translation Phenylpropanoids Binds to ribosomal peptidyl transfer center Chloramphenicol, 1947 preventing peptide translocation/ binds to rrn, cmlA, marA, ompF, S6, L3, L6, L14, L16, L25, L26, L27, but ompRpreferentially to L16 Tetracyclines, 1948, Binding to 30S ribosomal subunit, "A" site clmA (cmr), mar, ompF type II polyketides on 30S subunit, blocks peptide elongation, Minocycline strongest binding to S7 Doxycycline Macrolides (type I polyketides) Binding to 50 S ribosomal subunit, 23S rRNA, blocks peptide translocation, L15, Erythromycin, 1950 rrn, rplC, rplD, rplV, Carbomycin L4, L12 Spiramycin, etc Aminoglycosides Irreversible binding to 30S ribosomal Streptomycin, 1944 subunit, prevents translation or causes rpsL, strC,M, ubiF Neomycin mistranslation of mRNA/16S rRNA atpA-E, ecfB, hemAC,D,E,G, topA, Spectinomycin rpsC,D,E, rrn, spcB Kanamycin atpA-atpE, cpxA, ecfB, hemA,B,L, topA Kasugamycin ksgA,B,C,D, rplB,K, rpsI,N,M,R Gentamicin, 1963 rplF, ubiF **Amikacin** срхА Paromycin rpsL Lincosamides Binding to 50 S ribosomal subunit, blocks Lincomycin, 1955 peptide translocation linB, rplN,O, rpsG Clindamycin Streptogramins 2 components, Streptogramins A&B, bind Virginiamycin, 1955 to the 50S ribosomal subunit blocking Pristinamycin peptide translocation and peptide bond Synercid: quinupristin formation /dalfopristin **Fusidanes** Inhibition of elongation factor G (EF-G) fusA Fusidic Acid prevents peptide translocation Inhibition of elongation factor TU (EF-Tu), Kirromycin tufA,B prevents peptide bond formation (Mocimycin) Binds to and inhibits EF-TU Pulvomycin Sulfur-containing antibiotic, inhibits protein Thiopeptin rplEsynthesis, EF-G Tiamulin Inhibits protein synthesis rplC, rplD

PCT/US00/34419 WO 01/48209

Inhibits termination process of protein Negamycin prfB

synthesis

Oxazolidinones 23S rRNA Linezolid

pdx Isoniazid nfnA,B Nitrofurantoin Inhibits protein synthesis, nitroreductases

> convert nitrofurantoin to highly reactive electrophilic intermediates which attack bacterial ribosomal proteins non-

specifically

Inhibition of isoleucyl tRNA synthetase-Pseudomonic Acids Mupirocin used for Staph, topical cream, nasal

(Bactroban)

Indolmycin Inhibits tryptophanyl-tRNA synthetase

trpS Viomycin rrmA (23S rRNA

methyltransferase; mutant has slow growth rate, slow chain elongation rate, and viomycin

resistance)

ileS

Binds to L11-23S RNA complex Thiopeptides Inhibits GTP hydrolysis by EF-G Thiostrepton Stimulates GTP hydrolysis by EF-G Micrococcin

Inhibitors of Cell Walls/Membranes

Inhibition of one or more cell wall **B-lactams** Penicillin, 1929 transpeptidases, endopeptidases, and

glycosidases (PBPs), of the 12 PBPs only 2 ampC, ampD, ampE, Ampicillin Methicillin, 1960 are essential: mrdA (PBP2) and ftsI (pbpB, envZ, galU, hipA, hipQ, ompC, ompF, PBP3)

ompR, ptsI, rfa, tolD, tolE tonB

pmrA

Cephalosporins, 1962

Mecillinam alaS, argS, crp, cyaA, envB, mrdA,B, (amdinocillin) Binds to and inactivates PBP2 (mrdA)

mreB.C.D

Inactivates PBP3 (fts1) Aztreonam (Furazlocillin)

Bacilysin, Tetaine Dipeptide, inhib glucosamine synthase dppA

Glycopeptides Inhib G+ cell wall syn, binds to terminal Vancomycin, 1955 D-ala-D-ala of pentapeptide, Prevents dephosphorylation and Polypeptides

Bacitracin regeneration of lipid carrier rfa Cyclic lipopeptide Disrupts multiple aspects of membrane function, including peptidoglycan Daptomycin, 1980

synthesis, lipoteichoic acid synthesis, and the bacterial membrane potential

Surfactant action disrupts cell membrane Cyclic polypeptides lipids, binds lipid A mioety of LPS Polymixin, 1939

Analogue of P-enolpyruvate, inhibits 1st murA, crp, cyaA glpT, Fosfomycin, 1969 step in peptidoglycan synthesis - UDP-NhipA, ptsI, uhpT

> acetylglucosamine enolpyruvyl transferase, murA. Also acts as

Immunosuppressant

Prevents formation of D-ala dimer, hipA, cycA Cycloserine inhibits D-ala ligase, ddlA,B

Alafosfalin phosphonodipeptide, cell wall synthesis pepA, tpp

inhibitor, potentiator of β-lactams

Inhibitors of Protein Processing/Transport

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Globomycin Inhibits signal peptidase II (cleaves

prolipoproteins subsequent to lipid

modification, lspA

lpp, dnaE

EXAMPLE 12

Transfer of Exogenous Nucleic Acid Sequences to other Bacterial Species Using the E. coli Expression Vectors or Expression Vectors Functional in Bacterial Species other than E. coli.

Molecule No. EcXA190, encoding a portion of the b3052 gene of Escherichia coli, was either transformed directly into Enterobacter cloacae, Salmonella typhimurium and/or Klebsiella pneumoniae or subcloned into an expression vector functional in these species and the subclones transformed into these organisms. Suitable expression vectors are well known in the art. These expression vectors were introduced into Enterobacter cloacae, Salmonella typhimurium and/or Klebsiella pneumoniae cells that were then assayed for growth inhibition according to the method of Example 1. After growth in liquid culture, cells were plated at various serial dilutions and a score determined by calculating the log difference in growth for INDUCED vs. UNINDUCED antisense RNA expression as determined by the maximum 10 fold dilution at which a colony was observed. If there was no effect of antisense RNA expression in one organism, the clone is given a score of zero "0" in that organism. In contrast, a score of "8" means that 10⁸ times more cells were required to observe a colony formed on the induced state than in the non-induced state under the conditions used and in that organism.

Expression vectors containing Molecule No. EcXA190 were found to inhibit bacterial growth in all four organisms when expression of the antisense RNA was induced with IPTG. A score of 4 was assigned for *Escherichia coli*, 6 for *Enterobacter cloacae*, and 8 for *Salmonella typhimurium* and 3 for *Klebsiella pneumoniae* (obvious additional growth defect as well). The protein encoded by this sequence may be used as a target sequence to screen candidate compound libraries as described above.

In addition, the above methods were validated using other antisense nucleic acids which inhibit the growth of *E. coli* which were identified using methods similar to those described above. Expression vectors which inhibited growth of *E. coli* upon induction of antisense RNA expression with IPTG were transformed directly into *Enterobacter cloacae*, *Klebsiella pneumonia* or *Salmonella typhimurium*. The transformed cells were then assayed for growth inhibition according to the method of Example 1. After growth in liquid culture, cells were plated at various serial dilutions and a score determined by calculating the log difference in growth for INDUCED vs. UNINDUCED antisense RNA expression as determined by the maximum 10 fold dilution at which

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a colony was observed. The results of these experiments are listed in Table V below. If there was no effect of antisense RNA expression in a microorganism, the clone is minus in Table V below. In contrast, a positive in Table V below means that at least 10 fold more cells were required to observe a colony on the induced plate than on the non-induced plate under the conditions used and in that microorganism.

<u>TABLE V</u>

<u>Sensitivity of Other Microorganisms to Antisense Nucleic Acids That Inhibit Proliferation in E. coli</u>

Mol. No.	S. typhimurium	E. cloacae	K. pneumoniae
EcXA001	+	+	-
EcXA004	+	-	-
EcXA005	+	+	+
EcXA006	-	-	-
EcXA007	-	+	•
EcXA008	+	•	+
EcXA009	-	-	-
EcXA010	+	+	+
EcXA011	-	+	-
EcXA012	-	+	- ,
EcXA013	+	+	+
EcXA014	+	+	-
EcXA015	+	+	+
EcXA016	+	+	, +
EcXA017	+	+	+
EcXA018	+	+	+
EcXA019	+	+	+
EcXA020	+	+	+
EcXA021	+	+	+
EcXA023	+	+	+
EcXA024	+	-	+
EcXA025	-		-
EcXA026	+	+	-
EcXA027	+	+	-
EcXA028	+	_	-
EcXA029	-	-	-
EcXA030	+	+	+
EcXA031	+	-	-
EcXA032	+	+	•
EcXA033	+	+	+
EcXA034	+	+	+ .
EcXA035	-	•	-
EcXA036	+	-	+
EcXA037	+	+	-
EcXA038	+	+	+
EcXA039	+	•	-
EcXA041	+	+	+
EcXA042	-	+	+

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Mol. No.	S. typhimurium	E. cloacae	K. pneumoniae
EcXA043	•	-	
EcXA044	-	-	-
EcXA045	+	+	+
EcXA046	-	-	-
EcXA047	+	+	-
EcXA048	-	-	•
EcXA049	+	-	-
EcXA050	-	-	-
EcXA051	+	-	-
EcXA052	+	-	
EcXA053	+	+	+
EcXA054	-	-	+
EcXA055	+	-	•
EcXA056	+	-	+
EcXA057	+	+	-
EcXA058	-	-	-
EcXA059	+	+	+
EcXA060	-	-	-
EcXA061		•	-
EcXA062	-	-	•
EcXA063	+	+	-
EcXA064	-		-
EcXA065	+	+	-
EcXA066	-	_	-
EcXA067	-	+	-
EcXA068	-		-
EcXA069	-	+	•
EcXA070	-	_	-
EcXA071	+	_	-
EcXA072	+	-	+
EcXA073	+	+	+
EcXA074	+	+	+
EcXA075	+	-	-
EcXA076	-	+	-
EcXA077	+	+	-
EcXA079	+	+	+
EcXA080	+	~	•
EcXA082	• '	+	•
EcXA083	-	-	<u> </u>
EcXA084	-	+	
EcXA086	-	-	-
EcXA087	-		-
EcXA088	-	•	-
EcXA089	-	-	-
EcXA090	-		-
EcXA091	-	-	-
EcXA092	-	•	-
EcXA093	-	-	-

Mol. No.	S. typhimurium	E. cloacae	K. pneumoniae
EcXA094	+	+	+
EcXA095	+	+	-
EcXA096	•	•	-
EcXA097	+	-	-
EcXA098	+	-	-
EcXA099	-	-	-
EcXA100		•	-
EcXA101	-	-	-
EcXA102	- 1	-	
EcXA103		+	-
EcXA104	+	4	+
EcXA106	+	+	•
EcXA107		-	-
EcXA108	-	-	-
EcXA109		-	-
EcXA110	+	+	-
EcXA111	, .	-	-
EcXA112	<u> </u>	+	-
EcXA113	+	+	+
EcXA114	 	+	_
EcXA115		+	_
EcXA116	+	+	<u> </u>
EcXA117	+	-	- 0
EcXA118		-	-
EcXA119	+	+	_
EcXA120	_		_
EcXA121	-	-	_
EcXA122	+	-	+
EcXA123	+	-	-
EcXA124			
EcXA125			
EcXA126	_	-	_
EcXA127	+	+	
EcXA128	<u> </u>		
EcXA129	-	+	
EcXA130	+	+	
EcXA130	-	<u> </u>	
EcXA132 EcXA133	 		
EcXA136		-	
EcXA130			-
EcXA137	+	-	-
EcXA138	-		-
EcXA139 EcXA140	+.	*	-
			-
EcXA141	+	-	<u> </u>
EcXA142		-	-
EcXA143		+	-
EcXA144	+	+	-
EcXA145	-	<u> </u>	•

Mol. No.	S. typhimurium	E. cloacae	K. pneumoniae
EcXA146	-	-	
EcXA147	-	-	-
EcXA148	-	-	-
EcXA149	+	+ .	+
EcXA150	-	-	-
EcXA151	+	-	-
EcXA152	-	-	-
EcXA153	+	+	-
EcXA154	_	-	-
EcXA155	-	-	ND
EcXA156	•	+	-
EcXA157	_	-	-
EcXA158	-	-	-
EcXA159	+	-	-
EcXA160	+	-	-
EcXA162		-	-
EcXA163	-	•	-
EcXA164	_	-	-
EcXA165	ю	-	-
EcXA166	-	-	-
EcXA167	•	-	-
EcXA168	-	-	-
EcXA169	-	+	-
EcXA171	-	-	-
EcXA172	-	-	-
EcXA173	-	-	-
EcXA174	-	•	•
EcXA175	, -	-	· -
EcXA176	-	-	-
EcXA178	-	-	-
EcXA179		-	-
EcXA180	+ .	-	-
EcXA181	•		•
EcXA182	-	-	-
EcXA183	-	-	•
EcXA184	-	-	-
EcXA185	-	-	
EcXA186	-	-	_
EcXA187	+.	+	+
EcXA189	+	•	-
EcXA190	. +	+	+
EcXA191	+	+	•
EcXA192	•	+	-

Thus, the ability of an antisense nucleic acid which inhibits the proliferation of *E. coli* to inhibit the growth of other organims may be evaluated by either transforming the antisense nucleic acid directly into other *Escherichia* species or inserting the antisense nucleic acid into expression

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vectors that are functional in other Gram negative species such as Enterobacter cloacae, Salmonella typhimurium, and/or Klebsiella pneumoniae. Similarly, the antisense nucleic acid can be inserted in expression vectors that are functional in Gram-positive species such as Staphylococcus aureus, Enterococcus faecalis and Streptococcus pneumoniae or other species.

Those skilled in the art will appreciate that a negative result in a heterologous microorganism does not mean that that microorganism is missing that gene nor does it mean that the gene is unessential. However, a positive result means that the heterologous microorganism contains a homologous gene which is required for proliferation of that microorganism. The homologous gene may be obtained using the methods described herein. Those cells that are inhibited by antisense may be used in cell-based assays as described herein for the identification and characterization of compounds in order to develop antibiotics effective in these microorganisms. Those skilled in the art will appreciate that an antisense molecule which works in the microorganism from which it was obtained will not always work in a heterologous microorganism.

EXAMPLE 13

Use of Identified Exogenous Nucleic Acid Sequences as Probes

The identified sequence of the present invention can be used as probes to obtain the sequence of additional genes of interest from a second organism. For example, probes to genes encoding potential bacterial target proteins may be hybridized to nucleic acids from other organisms including other bacteria and higher organisms, to identify homologous sequences. Such hybridization might indicate that the protein encoded by the gene to which the probe corresponds is found in humans and therefore not necessarily a good drug target. Alternatively, the gene can be conserved only in bacteria and therefore would be a good drug target for a broad spectrum antibiotic or antimicrobial.

Probes derived from the identified nucleic acid sequences of interest or portions thereof can be labeled with detectable labels familiar to those skilled in the art, including radioisotopes and non-radioactive labels, to provide a detectable probe. The detectable probe can be single stranded or double stranded and can be made using techniques known in the art, including *in vitro* transcription, nick translation, or kinase reactions. A nucleic acid sample containing a sequence capable of hybridizing to the labeled probe is contacted with the labeled probe. If the nucleic acid in the sample is double stranded, it can be denatured prior to contacting the probe. In some applications, the nucleic acid sample can be immobilized on a surface such as a nitrocellulose or nylon membrane. The nucleic acid sample can comprise nucleic acids obtained from a variety of sources, including genomic DNA, cDNA libraries, RNA, or tissue samples.

Procedures used to detect the presence of nucleic acids capable of hybridizing to the detectable probe include well known techniques such as Southern blotting, Northern blotting, dot blotting, colony hybridization, and plaque hybridization. In some applications, the nucleic acid capable of hybridizing to the labeled probe can be cloned into vectors such as expression vectors, sequencing vectors, or in

vitro transcription vectors to facilitate the characterization and expression of the hybridizing nucleic acids in the sample. For example, such techniques can be used to isolate, purify and clone sequences from a genomic library, made from a variety of bacterial species, which are capable of hybridizing to probes made from the sequences identified in Examples 5 and 6.

EXAMPLE 14

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Preparation of PCR Primers and Amplification of DNA

The identified E. coli genes corresponding directly to or located within the operon of nucleic acid sequences required for proliferation or portions thereof can be used to prepare PCR primers for a variety of applications, including the identification or isolation of homologous sequences from other species, for example S. typhimurium, E. cloacae, E. faecalis, S. pneumoniae, and K. pneumoniae, which contain part or all of the homologous genes. Because homologous genes are related but not identical in sequence, those skilled in the art will often employ degenerate sequence PCR primers. Such degenerate sequence primers are designed based on conserved sequence regions, either known or suspected, such as conserved coding regions. The successful production of a PCR product using degenerate probes generated from the sequences identified herein would indicate the presence of a homologous gene sequence in the species being screened. The PCR primers are at least 10 nucleotides, and preferably at least 20 nucleotides in length. More preferably, the PCR primers are at least 20-30 nucleotides in length. In some embodiments, the PCR primers can be more than 30 nucleotides in length. It is preferred that the primer pairs have approximately the same G/C ratio, so that melting temperatures are approximately the same. A variety of PCR techniques are familiar to those skilled in the art. For a review of PCR technology, see Molecular Cloning to Genetic Engineering White, B.A. Ed. in Methods in Molecular Biology 67: Humana Press, Totowa 1997. When the entire coding sequence of the target gene is known, the 5' and 3' regions of the target gene can be used as the sequence source for PCR probe generation. In each of these PCR procedures, PCR primers on either side of the nucleic acid sequences to be amplified are added to a suitably prepared nucleic acid sample along with dNTPs and a thermostable polymerase such as Taq polymerase, Pfu polymerase, or Vent polymerase. The nucleic acid in the sample is denatured and the PCR primers are specifically hybridized to complementary nucleic acid sequences in the sample. The hybridized primers are extended. Thereafter, another cycle of denaturation, hybridization, and extension is initiated. The cycles are repeated multiple times to produce an amplified fragment containing the nucleic acid sequence between the primer sites.

EXAMPLE 15

Inverse PCR

The technique of inverse polymerase chain reaction can be used to extend the known nucleic acid sequence identified in Examples 5 and 6. The inverse PCR reaction is described generally by Ochman et al., in Ch. 10 of PCR Technology: Principles and Applications for DNA Amplification, (Henry A. Erlich, Ed.) W.H. Freeman and Co. (1992). Traditional PCR requires two primers that are

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used to prime the synthesis of complementary strands of DNA. In inverse PCR, only a core sequence need be known.

Using the sequences identified as relevant from the techniques taught in Examples 5 and 6 and applied to other species of bacteria, a subset of exogenous nucleic sequences are identified that correspond to genes or operons that are required for bacterial proliferation. In species for which a genome sequence is not known, the technique of inverse PCR provides a method for obtaining the gene in order to determine the sequence or to place the probe sequences in full context to the target sequence to which the identified exogenous nucleic acid sequence binds.

To practice this technique, the genome of the target organism is digested with an appropriate restriction enzyme so as to create fragments of nucleic acid that contain the identified sequence as well as unknown sequences that flank the identified sequence. These fragments are then circularized and become the template for the PCR reaction. PCR primers are designed in accordance with the teachings of Example 15 and directed to the ends of the identified sequence. The primers direct nucleic acid synthesis away from the known sequence and toward the unknown sequence contained within the circularized template. After the PCR reaction is complete, the resulting PCR products can be sequenced so as to extend the sequence of the identified gene past the core sequence of the identified exogenous nucleic acid sequence identified. This process can be repeated iteratively if necessary. In this manner, the full sequence of each novel gene can be identified. Additionally the sequences of adjacent coding and noncoding regions can be identified.

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EXAMPLE 16

Identification of Genes Required for Staphylococcus aureus Proliferation

Genes required for proliferation in *Staphylococcus aureus* are identified according to the methods described above.

EXAMPLE 17

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Identification of Genes Required for Neisseria gonorrhoeae Proliferation

Genes required for proliferation in *Neisseria gonorrhoeae* are identified according to the methods described above.

EXAMPLE 18

Identification of Genes Required for Pseudomonas aeruginosa Proliferation

Genes required for proliferation in *Pseudomonas aeruginosa* are identified according to the methods described above.

EXAMPLE 19

Identification of Genes Required for Enterococcus faecalis Proliferation

Genes required for proliferation in *Enterococcus faecalis* are identified according to the methods described above.

EXAMPLE 20

Identification of Genes Required for Haemophilus influenzae Proliferation

Genes required for proliferation in *Haemophilus influenzae* are identified according to the methods described above.

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EXAMPLE 21

Identification of Genes Required for Salmonella typhimurium Proliferation

Genes required for proliferation in Salmonella typhimurium are identified according to the methods described above.

EXAMPLE 22

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Identification of Genes Required for Helicobacter pylori Proliferation

Genes required for proliferation in *Helicobacter pylori* are identified according to the methods described above.

EXAMPLE 23

Identification of Genes Required for Mycoplasma pneumoniae Proliferation

Genes required for proliferation in *Mycoplasma pneumoniae* are identified according to the methods described above.

EXAMPLE 24

Identification of Genes Required for Plasmodium ovale Proliferation

Genes required for proliferation in *Plasmodium ovale* are identified according to the methods described above.

EXAMPLE 25

Identification of Genes Required for Saccharomyces cerevisiae Proliferation

Genes required for proliferation in Saccharomyces cerevisiae are identified according to the methods described above.

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EXAMPLE 26

Identification of Genes Required for Entamoeba histolytica Proliferation

Genes required for proliferation in *Entamoeba histolytica* are identified according to the methods described above.

EXAMPLE 27

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Identification of Genes Required for Candida albicans Proliferation

Genes required for proliferation in *Candida albicans* are identified according to the methods described above.

EXAMPLE 28

Identification of Genes Required for Klebsiella pneumoniae Proliferation

Genes required for proliferation in *Klebsiella pneumoniae* are identified according to the methods described above.

EXAMPLE 29

Identification of Genes Required for Salmonella typhi Proliferation

Genes required for proliferation in Salmonella typhi are identified according to the methods described above.

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EXAMPLE 30

Identification of Genes Required for Salmonella paratyphi Proliferation

Genes required for proliferation in Salmonella paratyphi are identified according to the methods described above.

EXAMPLE 31

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Identification of Genes Required for Salmonella cholerasuis Proliferation

Genes required for proliferation in Salmonella cholerasuis are identified according to the methods described above.

EXAMPLE 32

Identification of Genes Required for Staphylococcus epidermis Proliferation

Genes required for proliferation in *Staphylococcus epidermis* are identified according to the methods described above.

EXAMPLE 33

Identification of Genes Required for Mycobacterium tuberculosis Proliferation

Genes required for proliferation in *Mycobacterium tuberculosis* are identified according to the methods described above.

EXAMPLE 34

Identification of Genes Required for Mycobacterium leprae Proliferation

Genes required for proliferation in *Mycobacterium leprae* are identified according to the methods described above.

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EXAMPLE 35

Identification of Genes Required for Treponema pallidum Proliferation

Genes required for proliferation in *Treponema pallidum* are identified according to the methods described above.

EXAMPLE 36

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Identification of Genes Required for Bacillus anthracis Proliferation

Genes required for proliferation in *Bacillus anthracis* are identified according to the methods described above.

EXAMPLE 37

Identification of Genes Required for Yersinia pestis Proliferation

Genes required for proliferation in *Yersinia pestis* are identified according to the methods described above.

EXAMPLE 38

Identification of Genes Required for Clostridium botulimum Proliferation

Genes required for proliferation in *Clostridium botulinum* are identified according to the methods described above.

EXAMPLE 39

Identification of Genes Required for Campylobacter jejuni Proliferation

Genes required for proliferation in *Campylobacter jejuni* are identified according to the methods described above.

EXAMPLE 40

Identification of Genes Required for Chlamydia trachomatis Proliferation

Genes required for proliferation in *Chlamydia trachomatis* are identified according to the methods described above.

It will be appreciated that genes required for proliferation of any microorganism of interest, including those specifically mentioned herein, may be identified according to the methods described above.

Use of Isolated Exogenous Nucleic Acid Fragments as Antisense Antibiotics

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In addition to using the identified sequences to enable screening of molecule libraries to identify compounds useful to identify antibiotics, the sequences themselves can be used as therapeutic agents. Specifically, the identified exogenous sequences in an antisense orientation can be provided to an individual to inhibit the translation of a bacterial target gene.

Generation of Antisense Therapeutics from Identified Exogenous Sequences

The sequences of the present invention can be used as antisense therapeutics for the treatment of bacterial infections or simply for inhibition of bacterial growth *in vitro* or *in vivo*. The therapy exploits the biological process in cells where genes are transcribed into messenger RNA (mRNA) that is then translated into proteins. Antisense RNA technology contemplates the use of antisense oligonucleotides complementary to a target gene that will bind to its target nucleic acid and decrease or inhibit the expression of the target gene. For example, the antisense nucleic acid may inhibit the translation or transcription of the target nucleic acid. In one embodiment, antisense oligonucleotides can be used to treat and control a bacterial infection of a cell culture containing a population of desired cells contaminated with bacteria. In another embodiment, the antisense oligonucleotides can be used to treat an organism with a bacterial infection.

Antisense oligonucleotides can be synthesized from any of the sequences of the present invention using methods well known in the art. In a preferred embodiment, antisense oligonucleotides are synthesized using artificial means. Uhlmann & Peymann, Chemical Rev. 90:543-584 (1990) review antisense oligonucleotide technology in detail. Modified or unmodified antisense oligonucleotides can be used as therapeutic agents. Modified antisense oligonucleotides

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are preferred since it is well known that antisense oligonucleotides are extremely unstable. Modification of the phosphate backbones of the antisense oligonucleotides can be achieved by substituting the internucleotide phosphate residues with methylphosphonates, phosphorothioates, phosphoramidates, and phosphate esters. Nonphosphate internucleotide analogs such as siloxane bridges, carbonate bridges, thioester bridges, as well as many others known in the art may also be used. The preparation of certain antisense oligonucleotides with modified internucleotide linkages is described in U.S. Patent No. 5,142,047.

Modifications to the nucleoside units of the antisense oligonucleotides are also contemplated. These modifications can increase the half-life and increase cellular rates of uptake for the oligonucleotides in vivo. For example, α -anomeric nucleotide units and modified nucleotides such as 1,2-dideoxy-d-ribofuranose, 1,2-dideoxy-1-phenylribofuranose, and N^4 , N^4 -ethano-5-methyl-cytosine are contemplated for use in the present invention.

An additional form of modified antisense molecules is found in peptide nucleic acids. Peptide nucleic acids (PNA) have been developed to hybridize to single and double stranded nucleic acids. PNA are nucleic acid analogs in which the entire deoxyribose-phosphate backbone has been exchanged with a chemically completely different, but structurally homologous, polyamide (peptide) backbone containing 2-aminoethyl glycine units. Unlike DNA, which is highly negatively charged, the PNA backbone is neutral. Therefore, there is much less repulsive energy between complementary strands in a PNA-DNA hybrid than in the comparable DNA-DNA hybrid, and consequently they are much more stable. PNA can hybridize to DNA in either a Watson/Crick or Hoogsteen fashion (Demidov et al., *Proc. Natl. Acad. Sci. U.S.A.* 92:2637-2641, 1995; Egholm, *Nature* 365:566-568, 1993; Nielsen et al., *Science* 254:1497-1500, 1991; Dueholm et al., *New J. Chem.* 21:19-31, 1997).

Molecules called PNA "clamps" have been synthesized which have two identical PNA sequences joined by a flexible hairpin linker containing three 8-amino-3,6-dioxaoctanoic acid units. When a PNA clamp is mixed with a complementary homopurine or homopyrimidine DNA target sequence, a PNA-DNA-PNA triplex hybrid can form which has been shown to be extremely stable (Bentin et al., *Biochemistry* 35:8863-8869, 1996; Egholm et al., *Nucleic Acids Res.* 23:217-222, 1995; Griffith et al., *J. Am. Chem. Soc.* 117:831-832, 1995).

The sequence-specific and high affinity duplex and triplex binding of PNA have been extensively described (Nielsen et al., Science 254:1497-1500, 1991; Egholm et al., J. Am. Chem. Soc. 114:9677-9678, 1992; Egholm et al., Nature 365:566-568, 1993; Almarsson et al., Proc. Natl. Acad. Sci. U.S.A. 90:9542-9546, 1993; Demidov et al., Proc. Natl. Acad. Sci. U.S.A. 92:2637-2641, 1995). They have also been shown to be resistant to nuclease and protease digestion (Demidov et al., Biochem. Pharm. 48:1010-1313, 1994). PNA has been used to inhibit gene expression (Hanvey et al., Science 258:1481-1485,1992; Nielsen et al., Nucl. Acids. Res., 21:197-200, 1993; Nielsen et al., Gene 149:139-145, 1994; Good & Nielsen, Science, 95: 2073-2076, 1998), to block restriction enzyme activity (Nielsen et al., supra., 1993), to act as an artificial transcription promoter (Mollegaard, Proc.

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Natl. Acad. Sci. U.S.A. 91:3892-3895, 1994) and as a pseudo restriction endonuclease (Demidov et al., Nucl. Acids. Res. 21:2103-2107, 1993). Recently, PNA has also been shown to have antiviral and antitumoral activity mediated through an antisense mechanism (Norton, Nature Biotechnol., 14:615-619, 1996; Hirschman et al., J. Investig. Med. 44:347-351, 1996). PNAs have been linked to various peptides in order to promote PNA entry into cells (Basu et al., Bioconj. Chem. 8:481-488, 1997; Pardridge et al., Proc. Natl. Acad. Sci. U.S.A. 92:5592-5596, 1995).

The antisense oligonucleotides contemplated by the present invention can be administered by direct application of oligonucleotides to a target using standard techniques well known in the art. The antisense oligonucleotides can be generated within the target using a plasmid, or a phage. Alternatively, the antisense nucleic acid may be expressed from a sequence in the chromosome of the target cell. For example, a promoter may be introduced into the chromosme of the target cell near the target gene such that the promoter directs teh transcription of the antisense nucleic acid. Alternatively, a nucleic acid containing the antisense sequence operably linked to a promoter may be introduced into the chromosome of the target cell. It is further contemplated that contemplated that the antisense oligonucleotide contemplated are incorporated in a ribozyme sequence to enable the antisense to specifically bind and cleave its target mRNA. For technical applications of ribozyme and antisense oligonucleotides see Rossi et al., Pharmacol. Ther. 50(2):245-254, (1991). The present invention also contemplates using a retron to introduce an antisense oligonucleotide to a cell. Retron technology is exemplified by U.S. Patent No. 5,405,775. Antisense oligonucleotides can also be delivered using liposomes or by electroporation techniques which are well known in the art.

The antisense nucleic acids of the present invention can also be used to design antibiotic compounds comprising nucleic acids which function by intracellular triple helix formation. Triple helix oligonucleotides are used to inhibit transcription from a genome. The sequences identified as required for proliferation in the present invention, or portions thereof, can be used as templates to inhibit microorganism gene expression in individuals infected with such organisms. Traditionally, homopurine sequences were considered the most useful for triple helix strategies. However, homopyrimidine sequences can also inhibit gene expression. Such homopyrimidine oligonucleotides bind to the major groove at homopurine:homopyrimidine sequences. Thus, both types of sequences based on the sequences of the present invention that are required for proliferation are contemplated for use as antibiotic compound templates.

The antisense oligonucleotides of this example employ the identified sequences of the present invention to induce bacterial cell death or at least bacterial stasis by inhibiting target nucleic acid transcription or translation. Antisense oligonucleotides containing from about 8 to 40 nucleotides of the sequences of the present invention have sufficient complementary to form a duplex with the target sequence under physiological conditions.

To kill bacterial cells or inhibit their growth, the antisense oligonucleotides are applied to the bacteria or to the target cells under conditions that facilitate their uptake. These conditions

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include sufficient incubation times of cells and oligonucleotides so that the antisense oligonucleotides are taken up by the cells. In one embodiment, an incubation period of 7-10 days is sufficient to kill bacteria in a sample. An optimum concentration of antisense oligonucleotides is selected for use.

The concentration of antisense oligonucleotides to be used can vary depending on the type of bacteria sought to be controlled, the nature of the antisense oligonucleotide to be used, and the relative toxicity of the antisense oligonucleotide to the desired cells in the treated culture. Antisense oligonucleotides can be introduced to cell samples at a number of different concentrations preferably between $1 \times 10^{-10} \text{M}$ to $1 \times 10^{-4} \text{M}$. Once the minimum concentration that can adequately control gene expression is identified, the optimized dose is translated into a dosage suitable for use *in vivo*. For example, an inhibiting concentration in culture of 1×10^{-7} translates into a dose of approximately 0.6 mg/kg body weight. Levels of oligonucleotide approaching 100 mg/kg body weight or higher may be possible after testing the toxicity of the oligonucleotide in laboratory animals. It is additionally contemplated that cells from the subject are removed, treated with the antisense oligonucleotide, and reintroduced into the subject. This range is merely illustrative and one of skill in the art are able to determine the optimal concentration to be used in a given case.

After the bacterial cells have been killed or controlled in a desired culture, the desired cell population may be used for other purposes.

EXAMPLE 41

The following example demonstrates the ability of an *E. coli* antisense oligonucleotide to act as a bactericidal or bacteriostatic agent to treat a contaminated cell culture system. The application of the antisense oligonucleotides of the present invention are thought to inhibit the translation of bacterial gene products required for proliferation.

The antisense oligonucleotide of this example corresponds to a 30 base phophorothioate modified oligodeoxynucelotide complementary to a nucleic acid involved in proliferation, such as Molecule Number EcXA118 (SEQ ID NO: 1). A sense oligodeoxynucelotide complementary to the antisense sequence is synthesized and used as a control. The oligonucleotides are synthesized and purified according to the procedures of Matsukura, et al., Gene 72:343 (1988). The test oligonucleotides are dissolved in a small volume of autoclaved water and added to culture medium to make a 100 micromolar stock solution.

Human bone marrow cells are obtained from the peripheral blood of two patients and cultured according standard procedures well known in the art. The culture is contaminated with the K-12 strain of *E. coli* and incubated at 37°C overnight to establish bacterial infection.

The control and antisense oligonucleotide containing solutions are added to the contaminated cultures and monitored for bacterial growth. After a 10 hour incubation of culture and oligonucleotides, samples from the control and experimental cultures are drawn and analyzed for the translation of the target bacterial gene using standard microbiological techniques well

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known in the art. The target E. coli gene is found to be translated in the control culture treated with the control oligonucleotide, however, translation of the target gene in the experimental culture treated with the antisense oligonucleotide of the present invention is not detected or reduced.

One way to determine if a gene is essential for proliferation in a host or virulence in a host is to construct a conditional allele of the gene an infectious organism. The host is then challenged with the organism under conditions in which the product of the gene is functional or non-functional or has reduced activity or where the gene product is absent or else present but at a reduced level. If the gene is essential for proliferation or virulence the infection of the host will be diminished or abolished under conditions in which the product of the gene is not functional or has reduced activity or where the gene product is absent or else present but at a reduced level.

Since expression of an antisense nucleic acid complementary to a gene required for proliferation also decreases the synthesis of the gene product, antisense nucleic acids may also be used to evaluate whether a gene is essential for the proliferation or virulence of an infectious organism in the host. In such methods, nucleic acids encoding an antisense molecule complementary to the desired target gene are introduced into the infectious organism. For exampe, plasmids comprising one of SEQ ID NOs: 1-93 or fragments thereof which inhibit proliferation, may be introduced into the infectious organism. In some embodiments, the antisense nucleic acid may be transcribed from the IPTG-inducible promoter in pLEX5BA or from other regulated promoters or vector systems.

E. coli is transformed with the nucleic acid encoding the antisense molecule by electroporation and grown in medium which selects for the presence of the vector from which the antisense nucleic acid is expressed. The essentiality of the target for each antisense nucleic acid is verified in microorganisms grown in culture using the techniques described herein.

The ability of antisense expression to block *E. coli* infection in an animal is tested using the rabbit model of bacterial meningitis. A spinal needle is surgically placed into the cisterna magna of New Zealand White rabbits. The rabbits are inoculated with 10⁵ to 10⁶ cells of a normally virulent *E. coli* strain expressing an antisense nucleic acid complementary to a gene required for proliferation. Repeated CSF sampling is undertaken to determine multiple parameters of injury and infection such as cytochemical abnormalities, intracranial pressure, cerebral edema, BBB permeability, cerebral perfusion pressure and recovery of viable *E. coli* cells. Control animals are given intravenous injections of saline, which will not induce expression of the antisense nucleic acid, while experimental animals are given IPTG in intravenous injections to induce expression of the antisense nucleic acid. Alternatively, expression of the antisense nucleic acid may be induced by intravenous infusion of IPTG at sub-toxic levels. If other promoters other than IPTG inducible promoters are used, the rabbits may be fed the inducer in their water.

The use of rabbits allows multiple CSF samples per animal (one rabbit can give up to 8 sequential samples without change in CSF pressure). Treated animals receive therapy from 2 hours

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post receiving inoculation up to several days. A typical efficacy study consists of 3 control animals and 3 treated animals.

The control animals in which expression of the antisense nucliec acid is not induced are not protected against infection with *E. coli* and there is a logarithmic increase in viable bacteria. In experimental animals, *E. coli* cells recovered from the site of infection are viable until antisense expression is subsequently induced. However, if the antisense nucleic acid is directed against a gene required for proliferation, after treatment with the inducer for antisense expression the *E. coli* cells infecting these rabbits will not multiply and fewer viable cells will be recovered from the site of infection. The *E. coli* cells recovered from the rabbits treated with the inducer are recovered, if still present, and assayed as above to determine if the promoter and gene are still present and functional. Conversely, if the antisense nucleic acid is not complementary to a gene required for proliferation, treatment of the rabbits with inducer will have no effect on *E. coli* viability.

EXAMPLE 42

A subject suffering from an *E. coli* infection is treated with the antisense oligonucleotide preparation of Example 39. The antisense oligonucleotide is provided in a pharmaceutically acceptable carrier at a concentration effective to inhibit the transcription or translation of the target nucleic acid. The present subject is treated with a concentration of antisense oligonucleotide sufficient to achieve a blood concentration of about 100 micromolar. The patient receives daily injections of antisense oligonucleotide to maintain this concentration for a period of 1 week. At the end of the week a blood sample is drawn and analyzed for the presence or absence of the organism using standard techniques well known in the art. There is no detectable evidence of E. coli and the treatment is terminated.

EXAMPLE 43

Preparation and use of Triple Helix Probes

The sequences of microorganism genes required for proliferation of the present invention are scanned to identify 10-mer to 20-mer homopyrimidine or homopurine stretches that could be used in triple-helix based strategies for inhibiting gene expression. Following identification of candidate homopyrimidine or homopurine stretches, their efficiency in inhibiting gene expression is assessed by introducing varying amounts of oligonucleotides containing the candidate sequences into a population of bacterial cells that normally express the target gene. The oligonucleotides may be prepared on an oligonucleotide synthesizer or they may be purchased commercially from a company specializing in custom oligonucleotide synthesis, such as GENSET, Paris, France.

The oligonucleotides can be introduced into the cells using a variety of methods known to those skilled in the art, including but not limited to calcium phosphate precipitation, DEAE-Dextran, electroporation, liposome-mediated transfection or native uptake.

Treated cells are monitored for a reduction in proliferation using techniques such as monitoring growth levels as compared to untreated cells using optical density measurements. The

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oligonucleotides that are effective in inhibiting gene expression in cultured cells can then be introduced in vivo using the techniques well known in that art at a dosage level shown to be effective.

In some embodiments, the natural (beta) anomers of the oligonucleotide units can be replaced with alpha anomers to render the oligonucleotide more resistant to nucleases. Further, an intercalating agent such as ethidium bromide, or the like, can be attached to the 3' end of the alpha oligonucleotide to stabilize the triple helix. For information on the generation of oligonucleotides suitable for triple helix formation see Griffin et al. (Science 245:967-971 (1989)).

EXAMPLE 44

Identification of Bacterial Strains from Isolated Specimens by PCR

Classical bacteriological methods for the detection of various bacterial species are time consuming and costly. These methods include growing the bacteria isolated from a subject in specialized media, cultivation on selective agar media, followed by a set of confirmation assays that can take from 8 to 10 days or longer to complete. Use of the identified sequences of the present invention provides a method to dramatically reduce the time necessary to detect and identify specific bacterial species present in a sample.

In one exemplary method, bacteria are grown in enriched media and DNA samples are isolated from specimens of, for example, blood, urine, stool, saliva or central nervous system fluid by conventional methods. A panel of PCR primers based on identified sequences unique to various species of microorganisms are then utilized in accordance with Example 12 to amplify DNA of approximately 100-200 nucleotides in length from the specimen. A separate PCR reaction is set up for each pair of PCR primers and after the PCR reaction is complete, the reaction mixtures are assayed for the presence of PCR product. The presence or absence of bacteria from the species to which the PCR primer pairs belong is determined by the presence or absence of a PCR product in the various test PCR reaction tubes.

Although the PCR reaction is used to assay the isolated sample for the presence of various bacterial species, other assays such as the Southern blot hybridization are also contemplated.

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WHAT IS CLAIMED IS:

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1. A purified or isolated nucleic acid sequence consisting essentially of one the sequence of nucleotides of SEQ ID NOs: 1-93, wherein expression of said nucleic acid in a microorganism is capable of inhibiting proliferation of a microorganism.

- 2. The nucleic acid sequence of Claim 1, wherein said nucleic acid sequence is complementary to at least a portion of the nucleotide sequence of the coding strand of a gene whose expression is required for proliferation of a microorganism.
- 3. The nucleic acid of Claim 1, wherein said nucleic acid sequence has a nucleotide sequence complementary to at least a portion of the nucleotide sequence of an RNA required for proliferation of a microorganism.
- 4. The nucleic acid of Claim 3, wherein the nucleotide sequence of said RNA encodes more than one gene product.
- 5. A purified or isolated nucleic acid comprising a fragment of one of the nucleotide seuqence of SEQ ID NOs.: 1-93, said fragment selected from the group consisting of fragments comprising at least 10, at least 20, at least 25, at least 30, at least 50 and more than 50 consecutive nucleotides of one of the nucleotide sequences of SEQ ID NOs: 1-93.
- 6. A vector comprising a promoter operably linked to the nucleic acid sequence of Claims 1,2,3,4, or 5.
- 7. The vector of Claim 6, wherein said promoter is active in a microorganism selected from the group consisting of Aspergillus fumigatus, Bacillus anthracis, Burkholderia cepacia, Campylobacter jejuni, Candida albicans, Candida glabrata (also called Torulopsis glabrata), Candida tropicalis, Candida parapsilosis, Candida guilliermondii, Candida krusei, Candida kefyr (also called Candida pseudotropicalis), Candida dubliniensis, Chlamydia pneumoniae, Chlamydia trachomatus, Clostridium botulinum, Clostridium difficile, Cryptococcus neoformans, Enterobacter cloacae, Enterococcus faecalis, Escherichia coli, Haemophilus influenzae, Helicobacter pylori, Klebsiella pneumoniae, Listeria monocytogenes, Mycobacterium leprae, Mycobacterium tuberculosis, Neisseria gonorrhoeae, Pseudomonas aeruginosa, Salmonella cholerasuis, Salmonella enterica, Salmonella paratyphi, Salmonella typhi, Salmonella typhimurium, Staphylococcus aureus, Klebsiella pneumoniae, Listeria monocytogenes, Moxarella catarrhalis, Shigella boydii, Shigella dysenteriae, Shigella flexneri, Shigella sonnei, Pseudomonas aeruginosa, Staphylococcus epidermidis, Streptococcus pneumoniae, Treponema pallidum, Yersinia pestis and any species falling within the genera of any of the above species.
 - 8. A host cell containing the vector of Claim 6.
- 9. A purified or isolated nucleic acid consisting essentially of the coding sequence of one of SEQ ID NOs: 106-112, 119-122, 134-160, 164-171, 179-265, 271-273, 275, and 279-286.

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10. A fragment of the nucleic acid of Claim 8, said fragment comprising at least 10, at least 20, at least 25, at least 30, at least 50 or more than 50 consecutive nucleotides of one of SEQ ID NOs: 106-112, 119-122, 134-160, 164-171, 179-265, 271-273, 275, and 279-286.

- 11. A vector comprising a promoter operably linked to the nucleic acid of Claim 9 or Claim 10.
- 12. A purified or isolated antisense nucleic acid comprising a nucleic acid sequence complementary to at least a portion of an intragenic sequence, intergenic sequence, sequences spanning at least a portion of two or more genes, 5' noncoding region, or 3' noncoding region within an operon comprising a proliferation-required gene whose activity or expression is inhibited by an antisense nucleic acid comprising one of SEQ ID NOs.: 1-93.
- 13. A purified or isolated nucleic acid comprising a nucleic acid having at least 70% identity to a sequence selected from the group consisting of SEQ ID NOs.: 1-93, fragments comprising at least 25 consecutive nucleotides of SEQ ID NOs.: 1-93, the sequences complementary to SEQ ID NOs.: 1-93 and the sequences complementary to fragments comprising at least 25 consecutive nucleotides of SEQ ID NOs.: 1-93 as determined using BLASTN version 2.0 with the default parameters.
- 14. The nucleic acid of Claim 13, wherein said nucleic acid is from an organism selected from the group consisting of Aspergillus fumigatus, Bacillus anthracis, Burkholderia cepacia, Campylobacter jejuni, Candida albicans, Candida glabrata (also called Torulopsis glabrata), Candida tropicalis, Candida parapsilosis, Candida guilliermondii, Candida krusei, Candida kefyr (also called Candida pseudotropicalis), Candida dubliniensis, Chlamydia pneumoniae, Chlamydia trachomatus, Clostridium botulinum, Clostridium difficile, Cryptococcus neoformans, Enterobacter cloacae, Enterococcus faecalis, Escherichia coli, Haemophilus influenzae, Helicobacter pylori, Klebsiella pneumoniae, Listeria monocytogenes, Mycobacterium leprae, Mycobacterium tuberculosis, Neisseria gonorrhoeae, Pseudomonas aeruginosa, Salmonella cholerasuis, Salmonella enterica, Salmonella paratyphi, Salmonella typhi, Salmonella typhimurium, Staphylococcus aureus, Klebsiella pneumoniae, Listeria monocytogenes, Moxarella catarrhalis, Shigella boydii, Shigella dysenteriae, Shigella flexneri, Shigella sonnei, Pseudomonas aeruginosa, Staphylococcus epidermidis, Streptococcus pneumoniae, Treponema pallidum, Yersinia pestis and any species falling within the genera of any of the above species.
- 15. A vector comprising a promoter operably linked to a nucleic acid encoding a polypeptide whose expression is inhibited by an antisense nucleic acid comprising one of SEQ ID NOs.: 1-93.
 - 16. A host cell containing the vector of Claim 15.
- 17. The vector of Claim 15, wherein said polypeptide comprises a polypeptide comprising a sequence selected from the group consisting of SEQ ID NOs: 299-305, 312-315, 327-353, 357-364, 372-458, 464-466, 468 and 472-479.

18. A purified or isolated polypeptide comprising a polypeptide whose expression is inhibited by an antisense nucleic acid comprising one of SEQ ID NOs.: 1-93, or a fragment selected from the group consisting of fragments comprising at least 5, at least 10, at least 20, at least 30, at least 40, at least 50, at least 60 or more than 60 consecutive amino acids of one of the said polypeptides.

- 19. The polypeptide of Claim 18, wherein said polypeptide comprises a polypeptide comprising one of SEQ ID NOs.: 299-305, 312-315, 327-353, 357-364, 372-458, 464-466, 468 and 472-479 or a fragment comprising at least 5, at least 10, at least 20, at least 30, at least 40, at least 50, at least 60 or more than 60 consecutive amino acids of a polypeptide comprising a sequence selected from the group consisting of SEQ ID NOs.: 299-305, 312-315, 327-353, 357-364, 372-458, 464-466, 468 and 472-479.
- 20. A purified or isolated polypeptide comprising a polypeptide having at least 25% identity to a polypeptide whose expression is inhibited by a sequence selected from the group consisting of SEQ ID NOs.: 1-93, or at least 25% identity to a fragment comprising at least 5, at least 10, at least 20, at least 30, at least 40, at least 50, at least 60 or more than 60 consecutive amino acids of a polypeptide whose expression is inhibited by a nucleic acid selected from the group consisting of SEQ ID NOs.: 1-93 as determined using FASTA version 3.0t78 with the default parameters.
- 21. The polypeptide of Claim 20, wherein said polypeptide has at least 25% identity to a polypeptide comprising one of SEQ ID NOs: 299-305, 312-315, 327-353, 357-364, 372-458, 464-466, 468 and 472-479 or at least 25% identity to a fragment comprising at least 5, at least 10, at least 20, at least 30, at least 40, at least 50, at least 60 or more than 60 consecutive amino acids of a polypeptide comprising one of SEQ ID NOs.: 299-305, 312-315, 327-353, 357-364, 372-458, 464-466, 468 and 472-479 as determined using FASTA version 3.0t78 with the default parameters.
- 22. An antibody capable of specifically binding the polypeptide of one of Claims 18-21.
- 23. A method of producing a polypeptide, comprising introducing a vector comprising a promoter operably linked to a nucleic acid encoding a polypeptide whose expression is inhibited by an antisense nucleic acid comprising one of SEQ ID NOs.: 1-93 into a cell and expressing said polypeptide.
 - 24. The method of Claim 23, further comprising the step of isolating said polypeptide.
- 25. The method of Claim 23, wherein said polypeptide comprises a sequence selected from the group consisting of SEQ ID NOs.: 299-305, 312-315, 327-353, 357-364, 372-458, 464-466, 468 and 472-479.

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26. A method of inhibiting proliferation of a microorganism comprising inhibiting the activity or reducing the amount of a gene product whose expression is inhibited by an antisense nucleic acid comprising a sequence selected from the group consisting of SEQ ID NOs.: 1-93 or inhibiting the activity or reducing the amount of a nucleic acid encoding said gene product.

- 27. The method of Claim 26, wherein said gene product comprises a polypeptide comprising a sequence selected from the group consisting of SEQ ID NOs.: 299-305, 312-315, 327-353, 357-364, 372-458, 464-466, 468 and 472-479.
- 28. A method for identifying a compound which influences the activity of a gene product required for proliferation, said gene product comprising a gene product whose expression is inhibited by an antisense nucleic acid comprising a sequence selected from the group consisting of SEQ ID NOs.: 1-93, said method comprising:

contacting said gene product with a candidate compound; and determining whether said compound influences the activity of said gene product.

- 29. The method of Claim 28, wherein said gene product is a polypeptide and said activity is an enzymatic activity.
 - 30. The method of Claim 28, wherein said gene product is a polypeptide and said activity is a carbon compound catabolism activity.
 - 31. The method of Claim 28, wherein said gene product is a polypeptide and said activity is a biosynthetic activity.
- 20 32. The method of Claim 28, wherein said gene product is a polypeptide and said activity is a transporter activity.
 - 33. The method of Claim 28, wherein said gene product is a polypeptide and said activity is a transcriptional activity.
- 34. The method of Claim 28, wherein said gene product is a polypeptide and said activity is a DNA replication activity.
 - 35. The method of Claim 28, wherein said gene product is a polypeptide and said activity is a cell division activity.
 - 36. A compound identified using the method of Claim 28.
- 37. The method of Claim 28, wherein said gene product is a polypeptide comprising a sequence selected from the group consisting of SEQ ID NOs.: 299-305, 312-315, 327-353, 357-364, 372-458, 464-466, 468 and 472-479.

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38. A method for identifying a compound or nucleic acid having the ability to reduce the activity or level of a gene product required for proliferation, said gene product comprising a gene product whose activity or expression is inhibited by an antisense nucleic acid comprising a sequence selected from the group consisting of SEQ ID NOs.: 1-93, said method comprising:

- (a) providing a target that is a gene or RNA, wherein said target comprises a nucleic acid encoding said gene product;
 - (b) contacting said target with a candidate compound or nucleic acid; and
 - (c) measuring an activity of said target.

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- 39. The method of Claim 38, wherein said target is a messenger RNA molecule and said activity is translation of said messenger RNA.
 - 40. The method of Claim 38, wherein said target is a messenger RNA molecule and said activity is transcription of a gene encoding said messenger RNA.
 - 41. The method of Claim 38, wherein said target is a gene and said activity is transcription of said gene.
 - 42. The method of Claim 38, wherein said target is a nontranslated RNA and said activity is processing or folding of said nontranslated RNA or assembly of said nontranslated RNA into a protein/RNA complex.
 - 43. The method of Claim 38, wherein said target gene or RNA encodes a polypeptide comprising a sequence selected from the group consisting of SEQ ID NOs.: 299-305, 312-315, 327-353, 357-364, 372-458, 464-466, 468 and 472-479.
 - 44. A compound or nucleic acid identified using the method of Claim 38.
 - 45. A method for identifying a compound which reduces the activity or level of a gene product required for proliferation of a microorganism, wherein the activity or expression of said gene product is inhibited by an antisense nucleic acid comprising a sequence selected from the group consisting of SEQ ID NOs.: 1-93, said method comprising the steps of:
 - (a) expressing a sub-lethal level of an antisense nucleic acid complementary to a nucleic acid encoding said gene product in a cell to reduce the activity or amount of said gene product in said cell, thereby producing a sensitized cell;
 - (b) contacting said sensitized cell with a compound; and
 - (c) determining whether said compound inhibits the growth of said sensitized cell.
 - 46. The method of Claim 45, wherein said determining step comprises determining whether said compound inhibits the growth of said sensitized cell to a greater extent than said compound inhibits the growth of a nonsensitized cell.
 - 47. The method of Claim 45, wherein said cell is selected from the group consisting of bacterial cells, fungal cells, plant cells, and animal cells.
 - 48. The method of Claim 45, wherein said cell is a Gram negative bacterium.

49. The method of Claim 45, wherein said cell is an E. coli cell.

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- 50. The method of Claim 45, wherein said cell is from an organism selected from the group consisting of Aspergillus fumigatus, Bacillus anthracis, Burkholderia cepacia, Campylobacter jejuni, Candida albicans, Candida glabrata (also called Torulopsis glabrata), Candida tropicalis, Candida parapsilosis, Candida guilliermondii, Candida krusei, Candida kefyr (also called Candida pseudotropicalis), Candida dublimiensis, Chlamydia pneumoniae, Chlamydia trachomatus, Clostridium botulinum, Clostridium difficile, Cryptococcus neoformans, Enterobacter cloacae, Enterococcus faecalis, Escherichia coli, Haemophilus influenzae, Helicobacter pylori, Klebsiella pneumoniae, Listeria monocytogenes, Mycobacterium leprae, Mycobacterium tuberculosis, Neisseria gonorrhoeae, Pseudomonas aeruginosa, Salmonella cholerasuis, Salmonella enterica, Salmonella paratyphi, Salmonella typhi, Salmonella typhimurium, Staphylococcus aureus, Klebsiella pneumoniae, Listeria monocytogenes, Moxarella catarrhalis, Shigella boydii, Shigella dysenteriae, Shigella flexneri, Shigella sonnei, Pseudomonas aeruginosa, Staphylococcus epidermidis, Streptococcus pneumoniae, Treponema pallidum, Yersinia pestis and any species falling within the genera of any of the above species.
- 51. The method of Claim 45, wherein said antisense nucleic acid is transcribed from an inducible promoter.
- 52. The method of Claim 51, further comprising the step of contacting said cell with a concentration of inducer which induces said antisense nucleic acid to a sub-lethal level.
- 20 53. The method of Claim 45, wherein growth inhibition is measured by monitoring optical density of a culture growth solution.
 - 54. The method of Claim 45, wherein said gene product is a polypeptide.
 - 55. The method of Claim 54, wherein said polypeptide comprises a sequence selected from the group consisting of SEQ ID NOs.: 299-305, 312-315, 327-353, 357-364, 372-458, 464-466, 468 and 472-479.
 - 56. The method of Claim 45, wherein said gene product is an RNA.
 - 57. A compound identified using the method of Claim 45.
 - 58. A method for inhibiting cellular proliferation comprising introducing a compound with activity against a gene whose activity or expression is inhibited by an antisense nucleic acid comprising a sequence selected from the group consisting of SEQ ID NOs.: 1-93 or a compound with activity against the product of said gene into a population of cells expressing said gene.
 - 59. The method of Claim 58, wherein said compound is an antisense nucleic acid comprising a sequence selected from the group consisting of SEQ ID NOs.: 1-93, or a proliferation-inhibiting portion thereof.
 - 60. The method of Claim 59, wherein said proliferation inhibiting portion of one of SEQ ID NOs.: 1-93 is a fragment comprising at least 10, at least 20, at least 25, at least 30, at least 50 or more than 51 consecutive nucleotides of one of SEQ ID NOs.: 1-93.

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61. The method of Claim 58, wherein said population is a population selected from the group consisting of bacterial cells, fungal cells, plant cells, and animal cells.

- 62. The method of Claim 58, wherein said population is a population of Gram negative bacteria.
 - 63. The method of Claim 58, wherein said population is a population of E. coli cells.
- 64. The method of Claim 58, wherein said population is a population selected from the group consisting of Aspergillus fumigatus, Bacillus anthracis, Burkholderia cepacia, Campylobacter jejuni, Candida albicans, Candida glabrata (also called Torulopsis glabrata), Candida tropicalis, Candida parapsilosis, Candida guilliermondii, Candida krusei, Candida kefyr (also called Candida pseudotropicalis), Candida dubliniensis, Chlamydia pneumoniae, Chlamydia trachomatus, Clostridium botulinum, Clostridium difficile, Cryptococcus neoformans, Enterobacter cloacae, Enterococcus faecalis, Escherichia coli, Haemophilus influenzae, Helicobacter pylori, Klebsiella pneumoniae, Listeria monocytogenes, Mycobacterium leprae, Mycobacterium tuberculosis, Neisseria gonorrhoeae, Pseudomonas aeruginosa, Salmonella cholerasuis, Salmonella enterica, Salmonella paratyphi, Salmonella typhi, Salmonella typhimurium, Staphylococcus aureus, Klebsiella pneumoniae, Listeria monocytogenes, Moxarella catarrhalis, Shigella boydii, Shigella dysenteriae, Shigella flexneri, Shigella sonnei, Pseudomonas aeruginosa, Staphylococcus epidermidis, Streptococcus pneumoniae, Treponema pallidum, Versinia pestis and any species falling within the genera of any of the above species.
- 65. The method of Claim 58, wherein said gene encodes a polypeptide comprising a sequence selected from the group consisting of SEQ ID NOs.: 299-305, 312-315, 327-353, 357-364, 372-458, 464-466, 468 and 472-479.
- 66. A preparation comprising an effective concentration of an antisense nucleic acid comprising a sequence selected from the group consisting of SEQ ID NOs.: 1-93, or a proliferation-inhibiting portion thereof in a pharmaceutically acceptable carrier.
- 67. The preparation of Claim 66, wherein said proliferation-inhibiting portion of one of SEQ ID NOs.: 1-93 comprises at least 10, at least 20, at least 25, at least 30, at least 50 or more than 50 consecutive nucleotides of one of SEQ ID NOs.: 1-93.
- 68. A method for inhibiting the activity or expression of a gene in an operon required for proliferation wherein the activity or expression of at least one gene in said operon is inhibited by an antisense nucleic acid comprising a sequence selected from the group consisting of SEQ ID NOs.: 1-93, said method comprising contacting a cell in a cell population with an antisense nucleic acid comprising at least a proliferation-inhibiting portion of said operon.
- 69. The method of Claim 68, wherein said antisense nucleic acid comprises a sequence selected from the group consisting of SEQ ID NOs.: 1-93 or a proliferation inhibiting portion thereof.

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70. The method of Claim 68, wherein said cell is contacted with said antisense nucleic acid by introducing a plasmid which expresses said antisense nucleic acid into said cell population.

- 71. The method of Claim 68, wherein said cell is contacted with said antisense nucleic acid by introducing a phage which expresses said antisense nucleic acid into said cell population.
- 72. The method of Claim 68, wherein said cell is contacted with said antisense nucleic acid by expressing said antisense nucleic acid from the chromosome of cells in said cell population.
- 73. The method of Claim 68, wherein said cell is contacted with said antisense nucleic acid by introducing a promoter adjacent to a chromosomal copy of said antisense nucleic acid such that said promoter directs the synthesis of said antisense nucleic acid.
- 74. The method of Claim 68, wherein said cell is contacted with said antisense nucleic acid by introducing a retron which expresses said antisense nucleic acid into said cell population.
- 75. The method of Claim 68, wherein said cell is contacted with said antisense nucleic acid by introducing a ribozyme into said cell-population, wherein a binding portion of said ribozyme is complementary to said antisense oligonucleotide.
- 76. The method of Claim 68, wherein said cell is contacted with said antisense nucleic acid by introducing a liposome comprising said antisense oligonucleotide into said cell.
- 77. The method of Claim 68, wherein said cell is contacted with said antisense nucleic acid by electroporation of said antisense nucleic acid.
- 78. The method of Claim 68, wherein said antisense nucleic acid is a fragment comprising at least 10, at least 20, at least 25, at least 30, at least 50 or more than 50 consecutive nucleotides of one of SEQ ID NOs.: 1-93.
 - 79. The method of Claim 68 wherein said antisense nucleic acid is an oligonucleotide.
- 80. A method for identifying a gene which is required for proliferation of a microorganism comprising:
 - (a) contacting a microorganism other than E. coli with a nucleic acid selected from the group consisting of SEQ ID NOs.: 1-93;
 - (b) determining whether said nucleic acid inhibits proliferation of said microorganism; and
- (c) identifying the gene in said microorganism which is inhibited by said nucleic acid.
- 81. The method of Claim 80, wherein said microorganism is a Gram negative bacterium.
- 82. The method of Claim 80 wherein said microorganism is selected from the group consisting of Aspergillus fumigatus, Bacillus anthracis, Burkholderia cepacia, Campylobacter jejuni, Candida albicans, Candida glabrata (also called Torulopsis glabrata), Candida tropicalis, Candida parapsilosis, Candida guilliermondii, Candida krusei, Candida kefyr (also called Candida pseudotropicalis), Candida dubliniensis, Chlamydia pneumoniae, Chlamydia trachomatus,

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Clostridium botulinum, Clostridium difficile, Cryptococcus neoformans, Enterobacter cloacae, Enterococcus faecalis, Escherichia coli, Haemophilus influenzae, Helicobacter pylori, Klebsiella pneumoniae, Listeria monocytogenes, Mycobacterium leprae, Mycobacterium tuberculosis, Neisseria gonorrhoeae, Pseudomonas aeruginosa, Salmonella cholerasuis, Salmonella enterica, Salmonella paratyphi, Salmonella typhi, Salmonella typhimurium, Staphylococcus aureus, Klebsiella pneumoniae, Listeria monocytogenes, Moxarella catarrhalis, Shigella boydii, Shigella dysenteriae, Shigella flexneri, Shigella sonnei, Pseudomonas aeruginosa, Staphylococcus epidermidis, Streptococcus pneumoniae, Treponema pallidum, Yersinia pestis and any species falling within the genera of any of the above species.

- 83. The method of Claim 80, further comprising introducing said nucleic acid into a vector functional in said microorganism prior to introducing said inhibitory nucleic acid into said microorganism.
- 84. A method for identifying a compound having the ability to inhibit proliferation of a microorganism comprising:
 - (a) identifying in a first microorganism a homolog of a gene or gene product present in a second microorganism which is different than said first microorganism, wherein the activity or level of said gene or gene product is inhibited by a nucleic acid comprising a sequence selected from the group consisting of SEQ ID NOs. 1-93;
 - (b) identifying an inhibitory nucleic acid sequence which inhibits the activity of said homolog in said first microorganism;
 - (c) contacting said first microorganism with a sub-lethal level of said inhibitory nucleic acid, thus sensitizing said first microorganism;
 - (d) contacting the sensitized microorganism of step (c) with a compound; and
 - (e) determining whether said compound inhibits proliferation of said sensitized microorganism.
- 85. The method of Claim 84, wherein said determining step comprises determining whether said compound inhibits proliferation of said sensitized microorganism to a greater extent than said compound inhibits proliferation of a nonsensitized microorganism.
- 86. The method of Claim 84 wherein step (a) comprises identifying a homologous nucleic acid to a gene or gene product whose activity or level is inhibited by a nucleic acid selected from the group consisting of SEQ ID NOs. 1-93 or a nucleic acid encoding a homologous polypeptide to a polypeptide whose activity or level is inhibited by a nucleic acid selected from the group consisting of SEQ ID NOs. 1-93 by using an algorithm selected from the group consisting of BLASTN version 2.0 with the default parameters and FASTA version 3.0t78 algorithm with the default parameters to identify said homologous nucleic acid or said nucleic acid encoding a homologous polypeptide in a database.

87. The method of Claim 84 wherein said step (a) comprises identifying a homologous nucleic acid or a nucleic acid encoding a homologous polypeptide by identifying nucleic acids which hybridize to said first gene.

- 88. The method of Claim 84 wherein the step (a) comprises expressing a nucleic acid selected from the group consisting of SEQ ID NOs. 1-93 in said microorganism.
- 89. The method of Claim 84, wherein said inhibitory nucleic acid is an antisense nucleic acid.
- 90. The method of Claim 84, wherein said inhibitory nucleic acid comprises an antisense nucleic acid to a portion of said homolog.
- 91. The method of Claim 84, wherein said inhibitory nucleic acid comprises an antisense nucleic acid to a portion of the operon encoding said homolog.
- 92. The method of Claim 84, wherein the step of contacting the first microorganism with a sub-lethal level of said inhibitory nucleic acid comprises directly contacting said microorganism with said inhibitory nucleic acid.
- 93. The method of Claim 84, wherein the step of contacting the first microorganism with a sub-lethal level of said inhibitory nucleic acid comprises expressing an antisense nucleic acid to said homolog in said microorganism.
 - 94. The method of Claim 84, wherein said gene product comprises a polypeptide comprising a sequence selected from the group consisting of SEQ ID NOs.: 299-305, 312-315, 327-353, 357-364, 372-458, 464-466, 468 and 472-479.
 - 95. A compound identified using the method of Claim 84.
 - 96. A method of identifying a compound having the ability to inhibit proliferation comprising:
 - (a) contacting a microorganism other than E. coli with a sub-lethal level of a nucleic acid comprising a sequence selected from the group consisting of SEQ ID NOs. 1-93 or a portion thereof which inhibits the proliferation of E. coli, thus sensitizing said microorganism;
 - (b) contacting the sensitized microorganism of step (a) with a compound; and
 - (c) determining whether said compound inhibits proliferation of said sensitized microorganism.
 - 97. The method of Claim 96, wherein said determining step comprises determining whether said compound inhibits proliferation of said sensitized microorganism to a greater extent than said compound inhibits proliferation of a nonsensitized microorganism.
 - 98. A compound identified using the method of Claim 96.

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99. A method for identifying a compound having activity against a biological pathway required for proliferation comprising:

- (a) sensitizing a cell by expressing a sub-lethal level of an antisense nucleic acid complementary to a nucleic acid encoding a gene product required for proliferation, wherein the activity or expression of said gene product is inhibited by an antisense nucleic acid comprising a sequence selected from the group consisting of SEQ ID NOs.: 1-93, in said cell to reduce the activity or amount of said gene product;
 - (b) contacting the sensitized cell with a compound; and

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- (c) determining whether said compound inhibits the growth of said sensitized cell.
- 100. The method of Claim 99, wherein said determining step comprises determining whether said compound inhibits the growth of said sensitized cell to a greater extent than said compound inhibits the growth of a nonsensitized cell.
- 101. The method of Claim 99, wherein said cell is selected from the group consisting of bacterial cells, fungal cells, plant cells, and animal cells.
 - 102. The method of Claim 99, wherein said cell is a Gram negative bacterium.
 - 103. The method of Claim 99, wherein said Gram negative bacterium is E. coli.
- 104. The method of Claim 99, wherein said cell is selected from the group consisting of Aspergillus fumigatus, Bacillus anthracis, Burkholderia cepacia, Campylobacter jejuni, Candida albicans, Candida glabrata (also called Torulopsis glabrata), Candida tropicalis, Candida parapsilosis, Candida guilliermondii, Candida krusei, Candida kefyr (also called Candida pseudotropicalis), Candida dubliniensis, Chlamydia pneumoniae, Chlamydia trachomatus, Clostridium botulinum, Clostridium difficile, Cryptococcus neoformans, Enterobacter cloacae, Enterococcus faecalis, Escherichia coli, Haemophilus influenzae, Helicobacter pylori, Klebsiella pneumoniae, Listeria monocytogenes, Mycobacterium leprae, Mycobacterium tuberculosis, Neisseria gonorrhoeae, Pseudomonas aeruginosa, Salmonella cholerasuis, Salmonella enterica, Salmonella paratyphi, Salmonella typhi, Salmonella typhimurium, Staphylococcus aureus, Klebsiella pneumoniae, Listeria monocytogenes, Moxarella catarrhalis, Shigella boydii, Shigella dysenteriae, Shigella flexneri, Shigella sonnei, Pseudomonas aeruginosa, Staphylococcus epidermidis, Streptococcus pneumoniae, Treponema pallidum, Yersinia pestis and any species falling within the genera of any of the above species.
 - 105. The method of Claim 99, wherein said antisense nucleic acid is transcribed from an inducible promoter.
- 106. The method of Claim 99, further comprising contacting the cell with an agent which induces expression of said antisense nucleic acid from said inducible promoter, wherein said antisense nucleic acid is expressed at a sub-lethal level.

107. The method of Claim 99, wherein inhibition of proliferation is measured by monitoring the optical density of a liquid culture.

- 108. The method of Claim 99, wherein said gene product comprises a polypeptide comprising a sequence selected from the group consisting of SEQ ID NOs.: 299-305, 312-315, 327-353, 357-364, 372-458, 464-466, 468 and 472-479
 - 109. A compound identified using the method of Claim 99.
- 110. A method for identifying a compound having the ability to inhibit cellular proliferation comprising:
 - (a) contacting a cell with an agent which reduces the activity or level of a gene product required for proliferation of said cell, wherein said gene product is a gene product whose activity or expression is inhibited by an antisense nucleic acid comprising a sequence selected from the group consisting of SEQ ID NOs.: 1-93;
 - (b) contacting said cell with a compound; and
 - (c) determining whether said compound reduces proliferation of said contacted cell.
- 111. The method of Claim 110, wherein said determining step comprises determining whether said compound reduces proliferation of said contacted cell to a greater extent than said compound reduces proliferation of cells which have not been contacted with said agent.
- 112. The method of Claim 110, wherein said agent which reduces the activity or level of a gene product required for proliferation of said cell comprises an antisense nucleic acid to a gene or operon required for proliferation.
- 113. The method of Claim 110, wherein said agent which reduces the activity or level of a gene product required for proliferation of said cell comprises a compound known to inhibit growth or proliferation of a microorganism.
- 114. The method of Claim 110, wherein said cell contains a mutation which reduces the activity or level of said gene product required for proliferation of said cell.
- 115. The method of Claim 114, wherein said mutation is a temperature sensitive mutation.
- 116. The method of Claim 110, wherein said gene product comprises a polypeptide comprising a sequence selected from the group consisting of SEQ ID NOs.: 299-305, 312-315, 327-353, 357-364, 372-458, 464-466, 468 and 472-479
 - 117. A compound identified using the method of Claim 110.

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118. A method for identifying the biological pathway in which a proliferation-required gene or its gene product lies, wherein said gene or gene product comprises a gene or gene product whose activity or expression is inhibited by an antisense nucleic acid comprising a sequence selected from the group consisting of SEQ ID NOs.: 1-93, said method comprising:

- (a) expressing a sub-lethal level of an antisense nucleic acid which inhibits the activity of said proliferation-required gene or gene product in a cell;
- (b) contacting said cell with a compound known to inhibit growth or proliferation of a microorganism, wherein the biological pathway on which said compound acts is known; and
 - (c) determining whether said cell is sensitive to said compound.
- 119. The method of Claim 118, wherein said determining step comprises determining whether said cell has a substantially greater sensitivity to said compound than a cell which does not express said sub-lethal level of said antisense nucleic acid and wherein said gene or gene product lies in the same pathway on which said compound acts if said cell expressing said sub-lethal level of said antisense nucleic acid has a substantially greater sensitivity to said compound than said cell which does not express said sub-lethal level of said antisense nucleic acid.
- 120. The method of Claim 118, wherein said gene product comprises a polypeptide comprising a sequence selected from the group consisting of SEQ ID NOs.: 299-305, 312-315, 327-353, 357-364, 372-458, 464-466, 468 and 472-479
- 121. A method for determining the biological pathway on which a test compound acts comprising:
 - (a) expressing a sub-lethal level of an antisense nucleic acid complementary to a proliferation-required nucleic acid in a cell, wherein the activity or expression of said proliferation-required nucleic acid is inhibited by an antisense nucleic acid comprising a sequence selected from the group consisting of SEQ ID NOs.: 1-93 and wherein the biological pathway in which said proliferation-required nucleic acid or a protein encoded by said proliferation-required polypeptide lies is known,
 - (b) contacting said cell with said test compound; and
 - (c) determining whether said cell is sensitive to said test compound.
- 122. The method of Claim 121, wherein said determining step comprises determining whether said cell has a substantially greater sensitivity to said test compound than a cell which does not express said sub-lethal level of said antisense nucleic acid.

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123. The method of Claim 121, further comprising:

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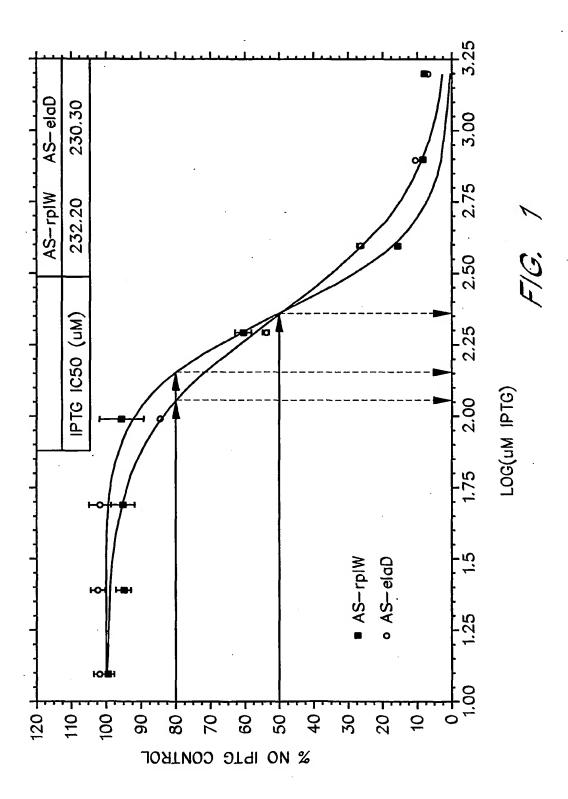
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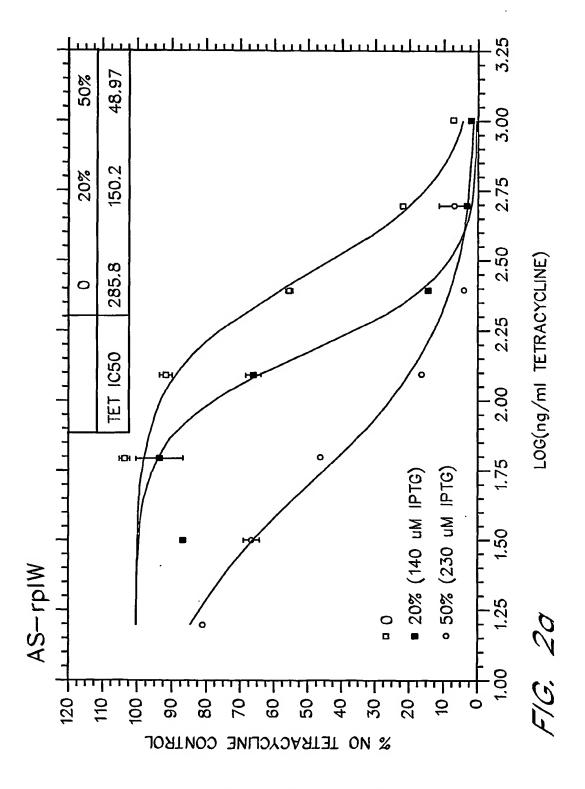
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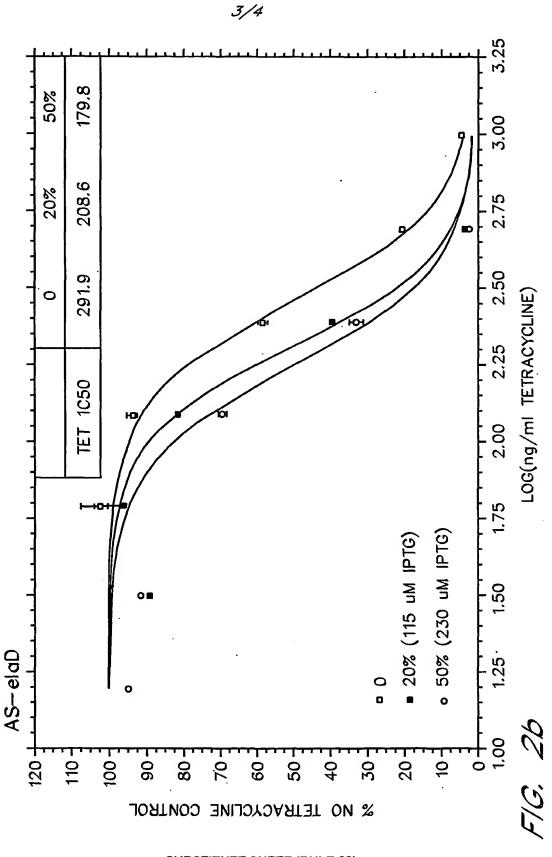
- (d) expressing a sub-lethal level of a second antisense nucleic acid complementary to a second proliferation-required nucleic acid in a second cell, wherein said second proliferation-required nucleic acid is in a different biological pathway than said proliferation-required nucleic acid in step (a); and
- (e) determining whether said second cell does not have a substantially greater sensitivity to said test compound than a cell which does not express said sub-lethal level of said second antisense nucleic acid, wherein said test compound is specific for the biological pathway against which the antisense nucleic acid of step (a) acts if said second cell does not have substantially greater sensitivity to said test compound.
- 124. A purified or isolated nucleic acid comprising a sequence selected from the group consisting of SEQ ID NOs.: 1-93.
- 125. A compound which interacts with a gene or gene product whose activity or expression is inhibited by an antisense nucleic acid comprising one of SEQ ID NOs.: 1-93 to inhibit proliferation.
- 126. A compound which interacts with a polypeptide whose expression is inhibited by an antisense nucleic acid comprising one of SEQ ID NOs.: 1-93 to inhibit proliferation.
- 127. A method for manufacturing an antibiotic comprising the steps of:
 screening one or more candidate compounds to identify a compound that reduces
 the activity or level of a gene product required for proliferation, said gene product
 comprising a gene product whose activity or expression is inhibited by an antisense nucleic
 acid comprising a sequence selected from the group consisting of SEQ ID NOs.: 1-93; and
 manufacturing the compound so identified.
- 128. The method of Claim 127, wherein said screening step comprises performing any one of the methods of Claims 28, 38, 45, 96, 99 and 110.
 - 129. A method for inhibiting proliferation of a microorganism in a subject comprising administering a compound that reduces the activity or level of a gene product required for proliferation of said microorganism, said gene product comprising a gene product whose activity or expression is inhibited by an antisense nucleic acid comprising a sequence selected from the group consisting of SEQ ID NOs.: 1-93 to said subject.
 - 130. The method of Claim 129 wherein said subject is selected from the group consisting of vertebrates, mammals, avians, and human beings.
 - 131. The method of Claim 129, wherein said gene product comprises a polypeptide comprising a sequence selected from the group consisting of SEQ ID NOs.: 299-305, 312-315, 327-353, 357-364, 372-458, 464-466, 468 and 472-479.



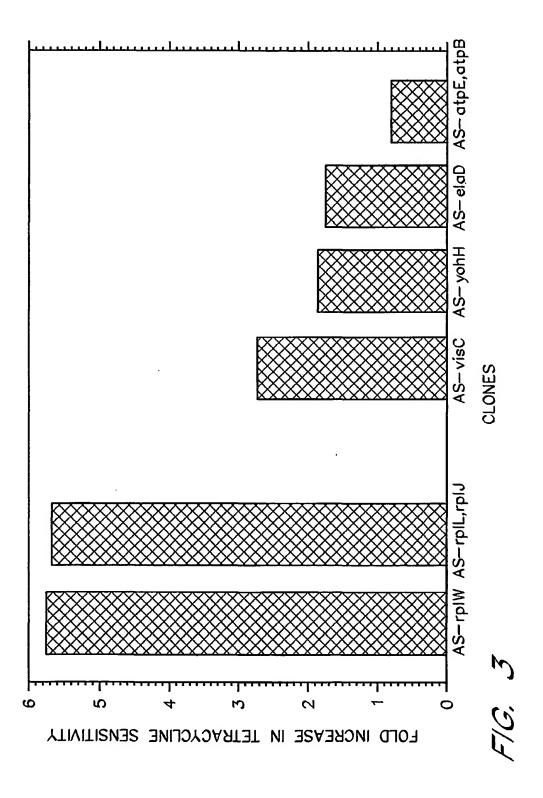
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SEQUENCE LISTING

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      OHLSEN, Kari L.
      ZYSKIND, Judith W.
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cttgtcatca tactgattgt actgttactc ataagtttca gcgcttatta acagtcagtc 120
tcaggggagg agcaatcctc ccttaccctt actcactaaa ttaggtcaaa gaatcaacga 180
tgtcaatcag ggcgatgcgg ttgtatcgcc cttaccactc ccagactttc gacggtgtaa 240
ccaccgcagg a
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<210> 46
<211> 286
<212> DNA
<213> Escherichia coli
<400> 46
caccqaaqcq agggcttgaa ggagaaqqqt tatqatqcqa cttqtcatca tactqattqt 60
actgttactc ataagtttca gcgcttatta acagtcagtc tcaggggagg agcaatcctc 120
ccttaccctt actcactaaa ttaggtcaaa gaatcaacga tgtcaatcag ggcgatgcgg 180
gtgtatcqcc cttaccactc ccagactttc gacgqtqtaa ccaccqcaqq aaqaqqqata 240
teccaetett caaeggggag tttttecaee aaetgacaat catgeg
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<210> 47
<211> 180
<212> DNA
<213> Escherichia coli
<400> 47
ccggggctga cgtgggcgat aatcgggtcg ccaggaatag ggcggcagca tttcgcaaag 60
gtgatcagca cgccatcggc acctttaatg ggcagatgtc cgtggctttg ggttgccggt 120
ggaatggagg cgtccccatg ttgcagattt ttcgcgacca ccacgctcat tqcgttacca 180
<210> 48
<211> 254
<212> DNA
<213> Escherichia coli
<400> 48
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tgtcgagcat acgcggcagc gccgactcgg aagatgaagt ccccagtaca atcagcagtt 60
 cttcacggat gtagcggata aatttgaaga tactgaaacc agtcgcttta gcgattgaac 120
 ccaataccag caccacaaac aggatacagg taatgtagaa acagataatc agctgcccca 180
 gttgcaccag tgtgccgacg ccgtatttac cgatggtaaa cgccattgcc ccgaacgcac 240
 caataggtgc caga
 <210> 49
 <211> 300
 <212> DNA
 <213> Escherichia coli
 <220×
 <221> misc feature
 <222> (1) ... (300)
 <223> n = A,T,C or G
 <400> 49
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coqcogagea ccaccogott acgcccgaag ctgtctgcca tcggcccgta gattaactgc 120
 cccaacgcaa agcccagaat ataagtactg agggtcatct gcgtactgcc cgncggtacg 180
 ccaaactgcg ctgaaattac cggtagcgcg ggcagataca tatcaatcga cagcggcatc 240
 aacatqqcca qcaqqccaaq gataaaaaca ataqcaaacg acgaatgctg tcgggtggtc 300
 <210> 50
 <211> 207
 <212> DNA
 <213> Escherichia coli
 <400> 50
 caacatetea tgtetggatt tgtagatata egtggaatte caattggtat ettttgtagg 60
 attcaacata tcatgtaagc gctgggagct taccaccata actggcccat catcgactga 120
 ggagaacagg ataaagatat tatcgtttcg tgttaattca ttcgtgttaa aggttcttaa 180
 attatcttca gtttctataa atatagg
 <210> 51
 <211> 213
 <212> DNA
 <213> Escherichia coli
 <400> 51
 ttctqtaatc aqaaaaqaa gaactggaat tttaataaat attatttctc tgggaacggg 60
 qqqqtataat caatatgacg agttgaatat tatatttttt ataagaatta tatgagatta 120
 aaqaaatctq ccgtaaagac agatttcttt aaaagataat tagagatttg cgacgttatg 180
 ataaactttt tgtacatcgt cgtcatcttc aag
 <210> 52
 <211> 381
 <212> DNA
 <213> Escherichia coli
 <400> 52
 tetgttagtg tattatecae tgeggeeett teegeegtet egeaaaeggg egetggettt 60
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 tatequeaqt ggtgetgteg tgatqegqte ttegcatgga cegcacaatg aagatacggt 180
 gettttgtat egtaettatt gtttetggtg egetgttaac egaggtaaat aataacegga 240
 qtctctccgg cgacaattta ctggtggtta acaaccttca gagcagcaag taagcccgaa 300
 tgccgccctt tgggcggcat attttagatt atccgattct gtttaaagtc acgcaaaaaa 360
 ccacccage gacgttcata g
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<210> 53

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<211> 154
<212> DNA
<213> Escherichia coli
<400> 53
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atgataaagg tgtagcatag atatttactt ggcgatttca ggatcttatc tgaaatcatg 120
ccaccaatcg gtccaccaat cattttcaga cagt
<210> 54
<211> 191
<212> DNA
<213> Escherichia coli
<400> 54
teettagtea ggtactgacg taetttaaaa tegetgteea ggttgteage gaattetttg 60
gtgttcgcaa accaggtaga gttccatggt tttacaatac ccaggcgaat accattagga 120
tgtactttct gacccattgc tagtctccag agtctcagcg atcggacaca accacagtga 180
tgtggctggt g
<210> 55
<211> 190
<212> DNA
<213> Escherichia coli
<400> 55
gctggtgccc gttttccatg ccagtggggc gacgcgggc aaggcactat ccggcaaggg 60
ttgegettea teageeataa teeggegaat gateeaegee geeceegaeg acattaaagg 120
ccgttcaagc agcggatcgt caggctgtaa gcgcaatttg cctgccttgc cgtggcgagc 180
aaacgcggta
<210> 56
<211> 402
<212> DNA
<213> Escherichia coli
<400> 56
aaaaaatgaa atteetettt gaegggeeaa tagegatatt ggeeattttt ttagegeaac 60
atttgeggca aatteeette teeatacagg tgtagtgcac egacegegac cacatatege 120
cccggcggca tggcgcgtaa tttatcccgc caggcgagat ttcgctgatg catcagcaca 180
tcgtacagcg actgactgaa cgtattgggc agcgttatat cattattttg cggcggtgca 240
ttcagccacc agetcatcat ttgttgcagc aaccgtgcgt tggtatgcca gtgggtcagc 300
gtategteca geagegeeag teetttgtea gggagetgga geaacatgge aatetggttt 360
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<210> 57
<211> 595
<212> DNA
<213> Escherichia coli
<220>
<221> misc feature
<222> (1) ... (595)
<223> n = A,T,C or G
<400> 57
aattaatcaq aqcaacqqta aaacaatqaa aqtqtaaaaa acacttttqc qccaattatq 60
gagaaaaaaa gaaaatttga tqqaqaqtga tqaqaqaata ttacaacacq atqattttqc 120
agagattatg aagaactata ccggatgact ggtgataaat aaagcaaata accaggatta 180
atctgtatta atttataaga aagcaactta atacccgcag aatgatttct gcgggtaagt 240
attagettat tttttegage attaateeeg egegtaatee caaegetaee aaeggattag 300
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qqaataacac atactctaca tcatqqqtta cqqtaaaacq ttcctctccq tcctqcqcca 360
gcaatgttcc tttctcaaac ggcataaaat tcagcgtgtc acttgccata tgcatttcga 420
aggacgega gtggcgagta atttgcgaaa ccacccgata acggagcggc ggtgttctca 480
cgataccgac actctcacca gatagcagcg cagcaattgc gctggcagtt actgcaaact 540
ggcgaagatc gttttgccca aagggcaacg ctttgccaag ttncagccgt acang
<210> 58
<211> 250
<212> DNA
<213> Escherichia coli
<400> 58
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tqcqcqqtga atatgcccga gcgcgatgta gtcggctggt ggaaagtttt gtgccggaaa 120
egegtecage gtgccaatat aaatgtcaeg caeggegtea ettttaetgg ceeecaeggt 180
cgttaaatgt cccgtggcga tgatgggcag aggctgatcg ccgcgcagtt tgcaggcatc 240
                                                                   250
ggcatagtgt
<210> 59
<211> 236
<212> DNA
<213> Escherichia coli
<400> 59
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gacgtttcga ccattttata acgggtaaaa ccaccatcaa catgagggaa atacatggca 120
ctgccaaaaa aacgcatatc tgtacactga ttctcgttat gttcaatgca gtatttgcag 180
tgaccgcacg gtttagacgg attaatggct accgtttgcc cttcatgtaa ttctga
<210> 60
<211> 92
<212> DNA
<213> Escherichia coli
<400> 60
gaaqaqatqt tcaqgttttc gttatcggca atggtatcga acttgtattt ctcatacttc 60
tcgtcaggcg tggagtacgc cgcgccacgg aa
<210> 61
<211> 62
<212> DNA
<213> Escherichia coli
<400> 61
tgtcgacatt cagcacttcc gggtattcgt cgcgcagggc aaatgtacag gttgaggagg 60
<210> 62
<211> 72
<212> DNA
<213> Escherichia coli
<400> 62
acttatcaaa ccatttttcc qcttcaccgg aggtctgcac ctgagcgatg gtgtcatcca 60
tcagcttttt ga
<210> 63
<211> 66
<212> DNA
<213> Escherichia coli
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<400> 63
aaacgcatgg cgcgtaaagg ttcaatcagt ccgatttcag cggtgtcgaa ctcgctaaat 60
tcttca
<210> 64
<211> 143
<212> DNA
<213> Escherichia coli
<220>
<221> misc_feature
<222> (1)...(143)
<223> n = A, T, C or G
<400> 64
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gacacaactc tttaatttct tccgccgcca tcgtagaggt cgcaaccgcg cctccgcaag 120
cgacaataat cttgcgtttc ata
<210> 65
<211> 210
<212> DNA
<213> Escherichia coli
gaggaaccgt gtgacacaca aagggtgatt attttccatt gcggcgtata atcctqqctc 60
accatcatgt attiticatgg ctaaaatact catcaccagt tittitgtita aaagetettg 120
tgctattgga gtggttaatg cattcagaaa gatatcgatt atttcatcga atccatacaa 180
catggagata taaagtccag gtgtttcgtt
                                                                   210
<210> 66
<211> 118
<212> DNA
<213> Escherichia coli
<400> 66
agagetgtga aggagaaaat acgaccacct ttaacggttt tagatacgcg gtttaccgcg 60
atcagetttt cetgeagtte gecagettgt ttttegatgt gagecatett acacetet
<210> 67
<211> 531
<212> DNA
<213> Escherichia coli
<220>
<221> misc_feature
<222> (1) ... (531)
<223> n = A,T,C or G
<400> 67
cettteaacg cagtagaggg gaatgnence tacggcateg geacegeget caatttetge 60
cagcatatag cccattccgt cttgatcggg cggaacatag gtgtcggcat cacttaaaaa 120
aacctggtcg caggtggcgt aattgaggcc attcatcagc gcaccacctt taccggtatt 180
tttttgegtg acggcaacaa ageggtegee ecatttgegt ttgactteeg ecatgacege 240
tteggtattg teegtggage egtegttaae geaaattace eggcaaaaat aangggtteg 300
cagtaantta tccagtgact ggcgccagac acgggccttt tttntncgca gntttaatgg 360
cgtcnaatac agcctttttt tttantgggt ttaccntnta nccgtnttta aaaacccata 420
gcaaccattg ttttngacct tcanaatnaa aaattcnggg ttttaaaagc gcgttttccq 480
gcaacttgnt ggacagggca aaaaattcct gcctgggtcg ccgnatctgn g
                                                                   531
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<210> 68

<211> 102 <212> DNA <213> Escherichia coli				
<400> 68 agegceggta acgcccgtta aatgttctcg gcgtaccgta gcggcatatt tcttccctgc			tcaacaggct	60 102
<210> 69 <211> 167 <212> DNA <213> Escherichia coli				
<pre><400> 69 aaaactcacc ttttttgttg ttatccctca aatgacctag acgtaattat gtaaaaataa cagctgttga aaaatcaaaa aactggaaaa</pre>	tgatgttcgt	cactgactat		
<210> 70 <211> 83 <212> DNA <213> Escherichia coli				
<400> 70 gccacgccca gcataaacag cgggatcgag accatcagca ccagcgataa tcc	g cetteaateg	gtacgcccag	tacacctttc	60 83
<210> 71 <211> 103 <212> DNA <213> Escherichia coli				
<220> <221> misc_feature <222> (1)(103) <223> n = A,T,C or G				
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<210> 72 <211> 121 <212> DNA <213> Escherichia coli				
<400> 72 tagettette cacattgteg aactgaacgt ggatttttte cgcacccagg caaacgcgcg g				
<210> 73 <211> 163 <212> DNA <213> Escherichia coli				
<400> 73 tagttattgg ctgttttgag aatgtaatct aatccgagaa tcacatgcaa tttattcata gcatagttga ccagaccgtc gagtcgctgc	aattcgtggg	atcgttcacg		

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<211> 106
<212> DNA
<213> Escherichia coli
<400> 74
aaaaccatga ggttattatg gccgatttga ggagggaaag agtaagagca gtttgttaaa 60
tgtacaacga cgattctccc accgggcgcg ttttaaagcg acggtg
<210> 75
<211> 319
<212> DNA
<213> Escherichia coli
<400> 75
ctggagattg agtagatatt cttgttcaga atgtatcagc ccgatggttc tacgattctt 60
aagecacgaa gagttcagat agtacaacgg catgtctctt ttgactatct ggcaaccegg 120
cagtgtgttc tctcacgcat cacaaaagca gcaggcataa aaaaacccgc ttgcgcggct 180
ttttcacaaa gcttcagcaa attggcgatt aagccagttt gttgatctgt gcagtcaggt 240
tagecttatg aegtgeaget ttgtttttgt ggateaaace tttageagec tgaeggteca 300
cgatcggttg catttcgtt
<210> 76
<211> 237
<212> DNA
<213> Escherichia coli
<400> 76
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cgttgtaggt gacaacgggg acgaatatta gcggcagagt gggaaggtgg caagaggcaa 120
aacgtaattt tetgegetat ttegacegtt tgeagagett ttaageaaat tggetatatt 180
ttgttgattt gcaagggtga tttttattca ggatcgcatt tacatctgat acaaccc
<210> 77
<211> 241
<212> DNA
<213> Escherichia coli
<400> 77
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atagegeata aaatateett ataattaaca agaaagaaaa ggeatattet etgeattate 120
attitetacg actgtcaaaa atcgctcatt tittaatgag titattigtt taatattatg 180
ggaaaaggtg atgcatttgg gagaggaaga gtattccccg gtcagacgac cggggaaggg 240
                                                                   241
<210> 78
<211> 89
<212> DNA
<213> Escherichia coli
<400> 78
cccggctggg ttttttcaag tttacgcagg ggtgcgggcg atcacttccg ggttgctggc 60
agcttcgcct ttcggcgaaa tgctgtggt
<210> 79
<211> 140
<212> DNA
<213> Escherichia coli
<400> 79
tegegaacac egtagtggat gtagttacce geagcatett egttgattge tttagaacca 60
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gaccacaggg tcaggttaga cggcgccagg tcagcagaac cgccgaggaa ttccggcaac 120
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<210> 80
<211> 189
<212> DNA
<213> Escherichia coli
<400> 80
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cacctgacgc gccagataaa taaagcgccc tttcgggttg gcgttaatgc gggctgaaag 180
ctgatccag
<210> 81
<211> 347
<212> DNA
<213> Escherichia coli
<400> 81
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tetggegtte ggegeggtgt ggegagataa atgeggteag caccaccagt ceggetteaa 180
ccatcaaatt cgccacttca ccgacgcgac ggatattctc tttacgatcg gcatcgctaa 240
aaccgagatc gctgcataat ccgtggcgaa cattgtcgcc atccagcaga tacgtactga 300
cgccgagttt atgtaacgcc tcctccagcg ccccggcgac cgttgat
<210> 82
<211> 67
<212> DNA
<213> Escherichia coli
<400> 82
ccctgacgat cagtgatagt cacgatggtg ttgttgaaag aagcatggat atgagccacg 60
ccgtcag
<210> 83
<211> 176
<212> DNA
<213> Escherichia coli
<400> 83
agcaaagcga gccgaacatg gtggcgaggc tgccgtaaag taaaaactgg gtcgccaact 60
cegggtgatc catcacgtat ttcacgaagt agagcgtcgc cccgccgcgc accacgttgg 120
agranging catcatetty aacgegeaca tgatgegeea etggetyttg eecage
<210> 84
<211> 632
<212> DNA
<213> Escherichia coli
<220>
<221> misc feature
<222> (1)...(632)
<223> n = A, T, C or G
<400> 84
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threenance ettenance nannananga nemencece enanceenat titigtitigg 120
aaanteegtt teaggaanag ettetgaate eeganegntt gataactgnn ggeeagagte 180
ataatgegca ccaataataa teageggnee ateggcagga ccataateag caacaatgnn 240
```

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nnggtagggg ccaccegtaa tggggacegt cctgcgaggt aactctggca ccgctactga 300
caaagacctc ttttatatat tctgcgggac ctattcagat tatcaatatt gtcnggcact 360
acgtggatgc acaagtttgt gtaagataac gaactgnttt ttctaattgc tcaggacttt 420
gcgtgtcggg gccgttgacg gtaatgcatt gacccagggt tggtaaaaaa taatcatagg 480
qaqtaaaaac acaaataata taataaaaqc caaqattatt tttttcatat qcaaaattat 540
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ttaaagatta agcangggat tataccaaaa ga
<210> 85
<211> 161
<212> DNA
<213> Escherichia coli
<400> 85
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atgatattca ctttggtgcc tggggtgacc tggctaaaga g
<210> 86
<211> 188
<212> DNA
<213> Escherichia coli
<400> 86
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cgaccagacc gcatttataa atacgtcgat agccaaacat atcgcccaga aacgaaaacg 120
agagcaggga gatgacaatg gcqatttqat aggcgttcac tacccagatg gaactggctg 180
gcgtggca
<210> 87
<211> 175
<212> DNA
<213> Escherichia coli
<400> 87
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gaccgcattt ataaatacgt cgatagccaa acatatcgcc cagaaacgaa aacgagagca 120
gggagatgac aatggcgatt tgataggcgt tcactaccca gatggaactg gctgg
<210> 88
<211> 194
<212> DNA
<213> Escherichia coli
<400> 88
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aacgaccaga ccqcatttat aaatacqtcq ataqccaaac atatcqccca qaaacqaaaa 120
cgagagcagg gagatgacaa tggcgatttg ataggcgttc actacccaga tggaactggc 180
tggcgtggca tgaa
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<210> 89
<211> 272
<212> DNA
<213> Escherichia coli
<400> 89
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tcctttactc taggttgaaa aaacaacagc qtcaataggc ctqccatqta cqaaqcqaqa 180
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<211> 245
<212> DNA
<213> Escherichia coli
<400> 90
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tcctttactc taggttgaaa aaacaacagc gtcaataggc ctgccatgta cgaagcgaga 180
totqtqaacc qctttccqgt tagccttttt tatcctgttg gatcttcttg atgatgttgg 240
<210> 91
<211> 203
<212> DNA
<213> Escherichia coli
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ccaqttatat caqtaqaaaa cctggttgtt gttaacagtc taaccggtca attttttatg 120
atttttttga taaaaattaa attttatttg ctttaatcac caccagatga cgttcgccat 180
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<210> 92
<211> 189
<212> DNA
<213> Escherichia coli
<220>
<221> misc feature
<222> (1)...(189)
<223> n = A,T,C or G
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gaacgtggcg ttaaatgtac cagttatatc agtagaaaac ctggttgntg ntaacagtct 120
aaccqqcaat tttttatgat ttttttgata aaaattaaat tttatttgct ttaatcacca 180
ccagatgac
                                                                   189
<210> 93
<211> 221
<212> DNA
<213> Escherichia coli
<400> 93
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agtegttatt actgettttt gttgtetace ageacegeca geaaaateac cacegetttg 120
acgatcatct ggtaatagga ggaaacacct aacaaattca atccattatt aaggaagcca 180
agaattaatg cgccgatcaa cgtcccaaca atgcgacctt t
<210> 94
<211> 117
<212> DNA
<213> Escherichia coli
<220>
<221> CDS
<222> (1) ... (117)
<400> 94
```

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_	_	_	-		_		_			tgc Cys	_	_		_	_	96
		_	_	caa Gln		tga *										117
<213 <213	0> 95 l> 13 2> Di 3> Es	332 NA	rich:	ia co	oli											
	0> L> CI 2> (1		. (13:	32)												
atg		aaa								agt Ser						48
										atc Ile						96
	_						_			ggt Gly		_	_	_	gta Val,	144
										acc Thr						192
	_					_		_	_	gct Ala 75				-	_	240
										att Ile						288
	_			_	_	~	_		_	aaa Lys	_					336
										ggt Gly						384
		_	_				_			ctg Leu	_		-			432
										gca Ala						480

145	150	155	160
gtt gta agt ctg gtc Val Val Ser Leu Val 165	. Thr Gly Thr Met		
cag att act gaa cga Gln Ile Thr Glu Arg 180			e Ile Phe
gcc ggt att gtc gcg Ala Gly Ile Val Ala 195			
caa gcg cgt caa ggc Gln Ala Arg Gln Gly 210			
gta tta gta ttt gca Val Leu Val Phe Ala 225			
caa cgc cgc att gtg Gln Arg Arg Ile Val 245	. Val Asn Tyr Ala		
gtc tat gct gca cag Val Tyr Ala Ala Glr 260			n Met Ala
ggg gta atc ccg gca Gly Val Ile Pro Ala 275			
acc atc gcg tca tgg Thr Ile Ala Ser Trg 290			
aca att tcg ctg tat Thr Ile Ser Leu Tyr 305			_
tat gcg tct gca ato Tyr Ala Ser Ala Ile 325	e Ile Phe Phe Cys		
ttc aac ccg cgt gaa Phe Asn Pro Arg Gli 340			y Ala Phe
gta cca gga att cgt Val Pro Gly Ile Arg 355			
gta atg acc cgc ctg Val Met Thr Arg Lev 370			
tgc ctg atc ccg gag Cys Leu Ile Pro Glu 385			

	ggt Gly															1248
	gct Ala															1296
	aag Lys															1332
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atg	0> 96 cgt Arg	tta			_		_	_	_				-	-	~~	48
	cgc Arg															96
	ggt Gly															144
	ttc Phe 50															192
	ttc Phe	Thr		Arg	Lys	Ala	Ala	Ile	Thr	Āla	Glu					240
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	ggc															384
	ggc Gly 130															432
taa																435

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ctg ccg aaa cac aag gca acg ctg ctt ggc ctg ggt ctg cgt cgt att
Leu Pro Lys His Lys Ala Thr Leu Leu Gly Leu Gly Leu Arg Arg Ile
ggt cac acc gta gag cgc gag gat act cct gct att cgc ggt atg atc
                                                                   144
Gly His Thr Val Glu Arg Glu Asp Thr Pro Ala Ile Arg Gly Met Ile
                             40
                                                                   180
aac gcg gtt tcc ttc atg gtt aaa gtt gag gag taa
Asn Ala Val Ser Phe Met Val Lys Val Glu Glu *
                         55
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<212> DNA
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<220>
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gcg gta aac cgc gta tct aaa acc gtt aaa ggt ggt cgt att ttc tcc
Ala Val Asn Arg Val Ser Lys Thr Val Lys Gly Gly Arg Ile Phe Ser
ttc aca gct ctg act gta gtt ggc gat ggt aac ggt cgc gtt ggt ttt
                                                                   144
Phe Thr Ala Leu Thr Val Val Gly Asp Gly Asn Gly Arg Val Gly Phe
ggt tac ggt aaa gcg cgt gaa gtt cca gca gcg atc cag aaa gcg atg
                                                                   192
Gly Tyr Gly Lys Ala Arg Glu Val Pro Ala Ala Ile Gln Lys Ala Met
gaa aaa gcc cgt cgc aat atg att aac gtc gcg ctg aat aac ggc act
                                                                   240
Glu Lys Ala Arg Arg Asn Met Ile Asn Val Ala Leu Asn Asn Gly Thr
                     70
                                          75
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ctg caa cac cct Leu Gln His Pro										288
cag ccg gct tcc Gln Pro Ala Ser 100										336
gcc gtt ctg gaa Ala Val Leu Glu 115		Gly Va								384
ggt tcc acc aac Gly Ser Thr Asn 130					Ala T					432
gaa aat atg aat Glu Asn Met Asn 145				Ala A						480
gtt gaa gaa att Val Glu Glu Ile									-	504
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100 105 110

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Ala Gly Leu Gln Phe * 115

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1 5 10 15

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ctg act cgt act ctc aac gat gct gtt gaa gtt aaa cat gca gat aat 144 Leu Thr Arg Thr Leu Asn Asp Ala Val Glu Val Lys His Ala Asp Asn 35 40

acc ctg acc ttc ggt ccg cgt gat ggt tac gca gac ggt tgg gca cag 192
Thr Leu Thr Phe Gly Pro Arg Asp Gly Tyr Ala Asp Gly Trp Ala Gin

gct ggt acc gcg cgt gcc ctg ctg aac tca atg gtt atc ggt gtt acc 240
Ala Gly Thr Ala Arg Ala Leu Leu Asn Ser Met Val Ile Gly Val Thr
65 70 75 80

gaa ggc ttc act aag aag ctg cag ctg gtt ggt gta ggt tac cgt gca 288 Glu Gly Phe Thr Lys Lys Leu Gln Leu Val Gly Val Gly Tyr Arg Ala 85 90 95

gcg gtt aaa ggc aat gtg att aac ctg tct ctg ggt ttc tct cat cct 336
Ala Val Lys Gly Asn Val Ile Asn Leu Ser Leu Gly Phe Ser His Pro
100 105 110

gtt gac cat cag ctg cct gcg ggt atc act gct gaa tgt ccg act cag 384 Val Asp His Gln Leu Pro Ala Gly Ile Thr Ala Glu Cys Pro Thr Gln 115 120 125

act gaa atc gtg ctg aaa ggc gct gat aag cag gtg atc ggc cag gtt 432 Thr Glu Ile Val Leu Lys Gly Ala Asp Lys Gln Val Ile Gly Gln Val 130 135 140

gca gcg gat ctg cgc gcc tac cgt cgt cct gag cct tat aaa ggc aag 480 Ala Ala Asp Leu Arg Ala Tyr Arg Arg Pro Glu Pro Tyr Lys Gly Lys 145 150 155 160

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	Pro Ile 85	_	ys Lys	Val	Thr 90	Leu	Arg	Gly	Glu	Arg 95	Met	
tgg gag ttc Trp Glu Phe												336
gac ttc cgt Asp Phe Arg 115												384
agc atg ggt Ser Met Gly 130		Glu G										432
aaa gtc gac Lys Val Asp 145					Ile							480
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						atc Ile	taa *								315
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atg		caa					aac Asn								48
							ctg Leu 25								96
_		_		_			 atc Ile				-	-		_	144
							gtg Val								192
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							aac Asn								288
_	_				_	_	cgt Arg 105			_	_		_		336
							gaa Glu								372
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	L> CI		. (14!	58)					·						
gtg		att					gat Asp	_							48

1				5				10					15		
				tct Ser											96
-	_		_	cgc Arg				_	_		-		_		144
				gca Ala											192
				tta Leu											240
				atc Ile 85											288
_				gtc Val							_		_		336
			_	acg Thr	-	_		_		_	_	_		_	384
-				gaa Glu			_	_	_				_		432
				ttt Phe											480
				att Ile 165											528
				ctg Leu											576
				agc Ser											624
				gtt Val											672
				cgc Arg											720
		-	_	tta Leu 245	_	_	 _		_		_	_	_	_	768

	_	_			acc Thr		_		_				_	816
					ttc Phe									864
					ggc Gly									912
_			_		gaa Glu 310			_		 _		 		960
					gtt Val									1008
					gcg Ala									1056
					gtc Val									1104
				_	atg Met					_			_	1152
					gca Ala 390									1200
					atc Ile									1248
				Thr	tct Ser		Gly		Gly					1296
	_				ata Ile	_		_			_	_	_	1344
			_	_	ggc									1392
					cga Arg 470							Thr		1440
_	gaa Glu			gat Asp 485	taa *									1458

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195 200 205 ege tte gee eeg ace tea tet eet gaa eag atg geg atg geg caa ege 672 Arg Phe Ala Pro Thr Ser Ser Pro Glu Gln Met Ala Met Ala Gln Arg 210 215 ctg aaa gaa tat ccg gat acg tgg gta cat acc cat ctc tgt gaa 720 Leu Lys Glu Glu Tyr Pro Asp Thr Trp Val His Thr His Leu Cys Glu aac aaa gat gaa att gcc tgg gtg aaa tcg ctt tat cct gac cat gat 768 Asn Lys Asp Glu Ile Ala Trp Val Lys Ser Leu Tyr Pro Asp His Asp ggt tat ctg gat gtt tac cat cag tac ggc ctg acc ggt aaa aac tgt 816 Gly Tyr Leu Asp Val Tyr His Gln Tyr Gly Leu Thr Gly Lys Asn Cys gte ttt get cae tge gte cat etc gaa gaa aaa gag tgg gat egt etc Val Phe Ala His Cys Val His Leu Glu Glu Lys Glu Trp Asp Arg Leu 280 age gaa ace aaa tee age att get tte tgt eeg ace tee aac ett tae 912 Ser Glu Thr Lys Ser Ser Ile Ala Phe Cys Pro Thr Ser Asn Leu Tyr 290 295 300 ctc ggc agc ggc tta ttc aac ttg aaa aaa gca tgg cag aag aaa gtt 960 Leu Gly Ser Gly Leu Phe Asn Leu Lys Lys Ala Trp Gln Lys Lys Val 305 310 315 aaa gtg ggc atg gga acg gat atc ggt gcc gga acc act ttc aac atg 1008 Lys Val Gly Met Gly Thr Asp Ile Gly Ala Gly Thr Thr Phe Asn Met 325 330 ctg caa acg ctg aac gaa gcc tac aaa gta ttg caa tta caa ggc tat 1056 Leu Gln Thr Leu Asn Glu Ala Tyr Lys Val Leu Gln Leu Gln Gly Tyr 340 345 cgc ctc tcg gca tat gaa gcg ttt tac ctg gcc acg ctc ggc gga gcg 1104 Arg Leu Ser Ala Tyr Glu Ala Phe Tyr Leu Ala Thr Leu Gly Gly Ala 355 aaa tot otg ggo ott gao gat ttg att ggo aac ttt tta oot ggo aaa 1152 Lys Ser Leu Gly Leu Asp Asp Leu Ile Gly Asn Phe Leu Pro Gly Lys 370 gag get gat tte gtg gtg atg gaa eee ace gee aet eeg eta eag eag 1200 Glu Ala Asp Phe Val Val Met Glu Pro Thr Ala Thr Pro Leu Gln Gln 385 390 395 ctg ege tat gac aac tet gtt tet tta gte gac aaa ttg tte gtg atg 1248 Leu Arg Tyr Asp Asn Ser Val Ser Leu Val Asp Lys Leu Phe Val Met 405 410 415

atg acg ttg ggc gat gac cgt tcg atc tac cgc acc tac gtt gat ggt 1296
Met Thr Leu Gly Asp Asp Arg Ser Ile Tyr Arg Thr Tyr Val Asp Gly
420 425 430

cgt ctg gtg tac gaa cgc aac taa 1320 Arg Leu Val Tyr Glu Arg Asn *

435

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195 200 205 ttc aat gat ttt att gac gct atg gct ggc ctg gtg tgt gcc gtg ttc Phe Asn Asp Phe Ile Asp Ala Met Ala Gly Leu Val Cys Ala Val Phe 210 215 ate gtt etg act tgt aat ate gtt ace ggt att atg etg gge ttt gtg Ile Val Leu Thr Cys Asn Ile Val Thr Gly Ile Met Leu Gly Phe Val 225 230 aca ctg gtc gta ggc cgc gtc ttt gca cgc gaa tgg caa aag ctg aat 768 Thr Leu Val Val Gly Arg Val Phe Ala Arg Glu Trp Gln Lys Leu Asn 245 250 att ggt acg gtg atc att act gcc gca ctg gtc gca ttt tac gcg ggt 816 Ile Gly Thr Val Ile Ile Thr Ala Ala Leu Val Ala Phe Tyr Ala Gly 260 265 ggt tgg gca atc taa 831 Gly Trp Ala Ile * 275 <210> 110 <211> 1401 <212> DNA <213> Escherichia coli <220> <221> CDS <222> (1) ... (1401) <400> 110 atg aat agc gaa ggg ggg aaa ccg ggg aat gta ctg acc gtt aac ggc Met Asn Ser Glu Gly Gly Lys Pro Gly Asn Val Leu Thr Val Asn Gly 10 aac tat acc gga aac aat ggc ctg atg acg ttc aac gcg acg ctg ggc 96 Asn Tyr Thr Gly Asn Asn Gly Leu Met Thr Phe Asn Ala Thr Leu Gly ggc gat aat teg eee ace gat aag atg aac gtg aaa ggc gat ace caa 144 Gly Asp Asn Ser Pro Thr Asp Lys Met Asn Val Lys Gly Asp Thr Gln ggg aac act cgc gtt cgg gtt gat aac att ggc ggc gtc ggt gca caa Gly Asn Thr Arg Val Arg Val Asp Asn Ile Gly Gly Val Gly Ala Gln 55 acg gtc aac ggt att gaa ctc att gag gtt ggc ggt aat tct gca ggt Thr Val Asn Gly Ile Glu Leu Ile Glu Val Gly Gly Asn Ser Ala Gly 70 aac tte geg etg ace ace gga act gte gaa get ggg get tae gte tae Asn Phe Ala Leu Thr Thr Gly Thr Val Glu Ala Gly Ala Tyr Val Tyr 85 acg ctg gct aaa ggg aag ggg aat gac gag aaa aac tgg tat ctg acc Thr Leu Ala Lys Gly Lys Gly Asn Asp Glu Lys Asn Trp Tyr Leu Thr 100 105

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				gtg Val												432
				atc Ile												480
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				tcg Ser												576
				agg Arg												624
_		_	_	cag Gln				_	_		_		_			672
				tgg Trp												720
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				agc Ser												816
		_		ggc Gly	_		_		_			_				864
				gtc Val												912
				acg Thr												960
				ggc Gly 325												1008
				atc Ile												1056
cgg	aaa	gac	gga	açg	cgc	att	gaa	acg	gaa	ggc	gac	gga	aat	gtg	caa	1104

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cgt gaa ggt gcg cgt aat ctc ggt gaa gta cgt acc ggg gtt Arg Glu Gly Ala Arg Asn Leu Gly Glu Val Arg Thr Gly Val 420 425 430	Glu Ala
aaa gta aat aac aac ctt agc ctg tgg ggg aat gtc ggt gtg Lys Val Asn Asn Asn Leu Ser Leu Trp Gly Asn Val Gly Val 435 440 445	
ggt gat aaa ggc tat agc gat act cag ggc atg ctg gga gtg Gly Asp Lys Gly Tyr Ser Asp Thr Gln Gly Met Leu Gly Val 450 455 460 \	
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				acg Thr												•	480
				tta Leu 165												!	528
				gac Asp													576
				ggt Gly													624
				gcc Ala													672
_	-	-	_	aag Lys			-							_			720
				caa Gln 245												,	768
cgc Arg	gag Glu	Gly ggg	ggg Gly 260	ttg Leu	gtt Val	acg Thr	gct Ala	gaa Glu 265	aat Asn	acg Thr	att Ile	atc Ile	ggt Gly 270	ggc Gly	aat Asn		816
				gga Gly													864
				ctc Leu													912
				gga Gly													960

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	Gly Thr Gly		cgc tat atc tat Arg Tyr Ile Tyr 350	
			agt gaa ggc aaa Ser Glu Gly Lys 365	
		Met Lys Glu	aca ggc aca ggc Thr Gly Thr Gly 380	
• • •	_	_	aat ctc gga act Asn Leu Gly Thr 395	
55 5 55		•	agt aat cag ggg Ser Asn Gln Gly	_
			gga gaa acc ggc Gly Glu Thr Gly 430	
			gag gtc aat aag Glu Val Asn Lys 445	
		Gly Val Gly	aac ctc aat att Asn Leu Asn Ile 460	
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			gcg aca tca tcg Ala Thr Ser Ser	
	Asn Val Gly		agc ggt atc gta Ser Gly Ile Val 510	
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		Val Asn Ile	tca acg gac agt Ser Thr Asp Ser 540	
			ttg cta cag gtc Leu Leu Gln Val 555	
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					tct Ser											1824
			_		acg Thr			_	_				_	_		1872
					gtt Val 630											1920
_					gct Ala	-						_	_	-		1968
					acg Thr											2016
	_				acc Thr			_	_	_			_	-	_	2064
_	_				gac Asp	_		_						_	-	2112
		_	_		aat Asn 710	_					_			_	_	2160
					ctg Leu											2208
_		_		_	agt Ser	_	_			-				_		2256
					acg Thr											2304
					gly											2352
_	_				acc Thr 790		_				-		_		_	2400
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acc atc att ttc Thr Ile Ile Phe 850		e Pro Ala Ala :		
tat atc agc gtc Tyr Ile Ser Val 865				
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gtg cct aaa ccg Val Pro Lys Pro 900				
ctc aat ttg ctg Leu Asn Leu Leu 915		p Ser His Val	_	
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gca cca ggt aat Ala Pro Gly Asn 980				
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ggc gca acg gcc Gly Ala Thr Ala 1010		a Lys Ile Gly (
gca atc aat acg Ala Ile Asn Thr 1025				
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cag atg ggt tcg act gtt ttg ttc aaa gag ggg gcg ctg acg gta aat Gln Met Gly Ser Thr Val Leu Phe Lys Glu Gly Ala Leu Thr Val Asn 1090 1095 1100	3312
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cag ggg tta ggc aga gga aat att gcc aat gac ggt ctg tta acg cta Gln Gly Leu Gly Arg Gly Asn Ile Ala Asn Asp Gly Leu Leu Thr Leu 1155 1160 1165	3504
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aac gag cag aaa aac ctg ggt gat gct tcc gtt atc aat aat ggc ctg Asn Glu Gln Lys Asn Leu Gly Asp Ala Ser Val Ile Asn Asn Gly Leu 1220 1225 1230	3696
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aac gat tcc gcg gcg tat cag ggt acg acg gat atc gtg ggg ggg gaa Asn Asp Ser Ala Ala Tyr Gln Gly Thr Thr Asp Ile Val Gly Glu 1265 1270 1275 1280	3840
att get tte ggt tee gae tet gee att aat atg gea agt caa cae att	

3936

aat atc cat aac agc ggt gtg atg tcg gga aat gtc acc act gca ggt

Asn Ile His Asn Ser Gly Val Met Ser Gly Asn Val Thr Thr Ala Gly 1300 1305 gat atg aac gtt atg cct ggg ggg ggc act gcg tgt cgc taa 3978 Asp Met Asn Val Met Pro Gly Gly Gly Thr Ala Cys Arg * 1320 <210> 112 <211> 756 <212> DNA <213> Escherichia coli <220> <221> CDS <222> (1)...(756) <400> 112 atg act gaa gca caa aga cat caa atc ctc ctg gaa atg ctc gca caa 48 Met Thr Glu Ala Gln Arg His Gln Ile Leu Leu Glu Met Leu Ala Gln ttg ggc ttt gtg acc gtt gag aaa gtc gtt gag cgt ctg gga att tcg 96 Leu Gly Phe Val Thr Val Glu Lys Val Val Glu Arg Leu Gly Ile Ser cet gee act geg ega ege gat ate aat aaa ett gae gaa age gge aaa Pro Ala Thr Ala Arg Arg Asp Ile Asn Lys Leu Asp Glu Ser Gly Lys 35 40 ctg aaa aaa gtg cgc aat ggc gca gaa gct att acc caa cag cgc ccg 192 Leu Lys Lys Val Arg Asn Gly Ala Glu Ala Ile Thr Gln Gln Arg Pro 50 55 cgc tgg acg ccg atg aat ctg cat cag gcg cag aat cac gat gaa aaa 240 Arg Trp Thr Pro Met Asn Leu His Gln Ala Gln Asn His Asp Glu Lys 70 65 75 gta cgt atc gct aaa gcg gcc tcg cag ctg gtt aat ccg ggc gaa agc 288 Val Arg Ile Ala Lys Ala Ala Ser Gln Leu Val Asn Pro Gly Glu Ser gta gtc atc aac tgc ggc tcc acc gcg ttt ctg ctt ggg cgg gaa atg 336 Val Val Ile Asn Cys Gly Ser Thr Ala Phe Leu Leu Gly Arg Glu Met 100 105 tgt ggc aag cca gtg caa atc atc act aat tat cta ccg ctg gca aat Cys Gly Lys Pro Val Gln Ile Ile Thr Asn Tyr Leu Pro Leu Ala Asn 115 120 tac ctg atc gat caa gaa cat gac agc gtg atc att atg ggc gga cag 432 Tyr Leu Ile Asp Gln Glu His Asp Ser Val Ile Ile Met Gly Gly Gln 130 tac aac aaa agt cag tee ate act tta age eeg cag ggc age gaa aac Tyr Asn Lys Ser Gln Ser Ile Thr Leu Ser Pro Gln Gly Ser Glu Asn 145 150 agt etc tat gee ggg cae tgg atg ttt ace age gga aaa ggg etg ace

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aag atg ctg agc Lys Met Leu Ser 195			s Leu		-	_	_	_	_	_	624
aag att ggc gaa Lys Ile Gly Glu 210			_			_	_	_			672
gat atg ctt atc Asp Met Leu Ile 225			_		_	_		_			720
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	cgc Arg															384
	cac His 130	-		_												432
_	cat His				_	_	_		_	_	_		_		_	480
	aaa Lys	-	_		_		_		_						_	528
	ttt Phe									_	_	_	-			576
	ctg Leu															624
_	gtc Val 210	_	_		_			_			_		_		_	672
	gtt Val		_	-		_	_	_	_	_	_		_		_	720
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Ala	Phe	Arg	Ala 20	Ser	Phe	His	Leu	His 25	Phe	Leu	Arg	Asn	His 30	Gly	Ile	
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		_			gat Asp			_				_				192
					ggt Gly 70											240
_	-		_		gcg Ala		_				_				_	288
					ttc Phe											336
_		_		_	atg Met		_		_	_				_	_	384
	_		-		ctg Leu											432
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		Tyr			tgt Cys											96
					ttt Phe											144

				aat Asn	_	_		_	_	_						192
	_	_	_	tcg Ser	_			_					_			240
				cat His 85		_								_	_	288
				acc Thr												336
cct Pro	geg Ala	gcc Ala 115	agt Ser	aat Asn	gca Ala	aaa Lys	gtg Val 120	aat Asn	gtt Val	tct Ser	gcg Ala	999 Gly 125	ggc	ggc Gly	ggt Gly	384
		_		aat Asn		_					_	_			_	432
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			_	att Ile		_	_	_								720
				cgg Arg 245												768
				aac Asn												816
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		ccg Pro														432

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380

aat tta ttg acg ctg tat ggt ggc tcg atg gtc gcg aat aat tat tac Asn Leu Leu Thr Leu Tyr Gly Gly Ser Met Val Ala Asn Asn Tyr Tyr

375

370

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														gat Asp		1344
				-		_		_				_		tat Tyr	_	1392
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	-	_	_							_	_			aac Asn		1584
_	-			_					_	_	_	-		gac Asp		1632
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					gga Gly							2064
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	l A				ggt Gly							2352
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				atg Met										288
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				att Ile										384
				gaa Glu										432
				ttt Phe 150										480
		_	_	aaa Lys	-	_	_	_	_				_	528
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								gat Asp					336
								tta Leu					384
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ctg ctg ctg ctc agt gaa gga gac gaa ctg cta tta ttg caa gat
Leu Leu Arg Leu Leu Ser Glu Gly Asp Glu Leu Leu Leu Gln Asp
ggc gta act gcc gca gtt gac ggt aac cgc tac ctt gaa agt ctg cgt
Gly Val Thr Ala Ala Val Asp Gly Asn Arg Tyr Leu Glu Ser Leu Arg
                             40
aat gcc ccc att aag gtc tat gcc ctg aac gaa gac ctt att gcc cgc
                                                                   192
Asn Ala Pro Ile Lys Val Tyr Ala Leu Asn Glu Asp Leu Ile Ala Arg
                         55
ggt ttg act ggt caa att tcg aac gac atc att ctc att gac tat act
Gly Leu Thr Gly Gln Ile Ser Asn Asp Ile Ile Leu Ile Asp Tyr Thr
                     70
gat ttc gtc aga ctt acg gtt aag cac ccc agc cag atg gcc tgg tga
Asp Phe Val Arg Leu Thr Val Lys His Pro Ser Gln Met Ala Trp
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<211> 360
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<213> Escherichia coli
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gca ggc cgg gaa ggt tta gat gct tta ctg gca act tcc gca tta act
Ala Gly Arg Glu Gly Leu Asp Ala Leu Leu Ala Thr Ser Ala Leu Thr
gac gat ctg gct gtc ttc ttt ata gct gat ggc gtt ttt cag ctg ctg
                                                                   144
Asp Asp Leu Ala Val Phe Phe Ile Ala Asp Gly Val Phe Gln Leu Leu
cca gga caa aag ccc gat gca gtg ctg gcg cgt gat tac att gcc act
                                                                   192
Pro Gly Gln Lys Pro Asp Ala Val Leu Ala Arg Asp Tyr Ile Ala Thr
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50 55 60 ttt aaa ttg ttg ggt ctg tac gac att gaa cag tgc tgg gtt tgt gcg Phe Lys Leu Leu Gly Leu Tyr Asp Ile Glu Gln Cys Trp Val Cys Ala get tea etg ege gaa ege ggg tta gat eeg eag aca eee ttt gtt gte 288 Ala Ser Leu Arg Glu Arg Gly Leu Asp Pro Gln Thr Pro Phe Val Val gaa gcc acg ccg ctc gaa gca gat gcc tta cgc cgc gaa ctc gcc aac Glu Ala Thr Pro Leu Glu Ala Asp Ala Leu Arg Arg Glu Leu Ala Asn 105 tac gat gtt att ttg agg ttt tga 360 Tyr Asp Val Ile Leu Arg Phe * 115 <210> 121 <211> 387 <212> DNA <213> Escherichia coli <220> <221> CDS <222> (1) ... (387) atg cgt ttt gcc atc gtg gtg acc ggg cca gca tac ggt acg caa cag Met Arg Phe Ala Ile Val Val Thr Gly Pro Ala Tyr Gly Thr Gln Gln 10 gcg agt agt gct ttt cag ttt gcg cag gcg ctg ata gca gat ggc cat 96 Ala Ser Ser Ala Phe Gln Phe Ala Gln Ala Leu Ile Ala Asp Gly His gag tta agc agc gtc ttt ttc tat cgg gaa ggg gtc tat aac gct aac 144 Glu Leu Ser Ser Val Phe Phe Tyr Arg Glu Gly Val Tyr Asn Ala Asn caa ttg acc tct ccg gca agt gac gaa ttt gac ctc gta cgg gcc tgg 192 Gln Leu Thr Ser Pro Ala Ser Asp Glu Phe Asp Leu Val Arg Ala Trp caa caa ctg aat gcg caa cat ggt gtg gcg ctg aat atc tgc gta gcg Gln Gln Leu Asn Ala Gln His Gly Val Ala Leu Asn Ile Cys Val Ala 70 gea gea tta ege egt gge gtt gtt gat gaa aeg gag gee gga aga etg Ala Ala Leu Arg Arg Gly Val Val Asp Glu Thr Glu Ala Gly Arg Leu 85 90 ggg ctg gct tcg tca aac ctt cag cag gga ttt acc tta agc qqa ctt Gly Leu Ala Ser Ser Asn Leu Gln Gln Gly Phe Thr Leu Ser Gly Leu ggg gcg ctg gcg gaa gcc tcg ctg acc tqt gac agg gtg qta cag ttc Gly Ala Leu Ala Glu Ala Ser Leu Thr Cys Asp Arg Val Val Gln Phe

120

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180 185 190 aaa aat cgt cag atc gtg ctg aat ctc tac gag aaa ggg atc ttc gat 624 Lys Asn Arg Gln Ile Val Leu Asn Leu Tyr Glu Lys Gly Ile Phe Asp 200 att aaa gat geg atc aac cag gtt get gac ege etg aac atc tec aaa Ile Lys Asp Ala Ile Asn Gln Val Ala Asp Arg Leu Asn Ile Ser Lys 210 215 cac act gtc tat ctc tac atc cgc cag ttc aag agc ggt gat ttc cag His Thr Val Tyr Leu Tyr Ile Arg Gln Phe Lys Ser Gly Asp Phe Gln 225 230 235 ggg caa gat aag taa 735 Gly Gln Asp Lys * <210> 123 <211> 255 <212> DNA <213> Escherichia coli <220> <221> CDS <222> (1)...(255) atg acc gat aaa atc cgt act ctg caa ggt cgc gtt gtt agc gac aaa 48 Met Thr Asp Lys Ile Arg Thr Leu Gln Gly Arg Val Val Ser Asp Lys 10 atg gag aaa too att gtt gtt gct atc gaa cgt ttt gtg aaa cac ccg Met Glu Lys Ser Ile Val Val Ala Ile Glu Arg Phe Val Lys His Pro 20 ate tac ggt aaa tte ate aag egt acg ace aaa etg cac gta cat gae 144 Ile Tyr Gly Lys Phe Ile Lys Arg Thr Thr Lys Leu His Val His Asp 40 gag aac aac gaa tgc ggt atc ggt gac gtg gtt gaa atc cgc gaa tgc 192 Glu Asn Asn Glu Cys Gly Ile Gly Asp Val Val Glu Ile Arg Glu Cys cgt ccg ctg tcc aag act aaa tcc tgg acg ctg gtt cgc gtt gta gag 240 Arg Pro Leu Ser Lys Thr Lys Ser Trp Thr Leu Val Arg Val Val Glu aaa gcg gtt ctg taa 255 Lys Ala Val Leu * <210> 124 <211> 192 <212> DNA

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gec egt gaa gea tte aag etg gea gea geg aaa etg eeg att aaa ace 3 Ala Arg Glu Ala Phe Lys Leu Ala Ala Lys Leu Pro Ile Lys Thr

cag ccg ggt aaa gtc ctg tat gaa atg gac ggt gtt ccg gaa gag ctg

Gln Pro Gly Lys Val Leu Tyr Glu Met Asp Gly Val Pro Glu Glu Leu

85

336

115 120 125

acc ttt gta act aag acg gtg atg taa 411
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<220> <221> CDS <222> (1)...(702)

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1 5 10 15

cca tgg aac tct acc tgg ttt gcg aac acc aaa gaa ttc gct gac aac 96 Pro Trp Asn Ser Thr Trp Phe Ala Asn Thr Lys Glu Phe Ala Asp Asn 20 25 30

ctg gac agc gat ttt aaa gta cgt cag tac ctg act aag gaa ctg gct 144 Leu Asp Ser Asp Phe Lys Val Arg Gln Tyr Leu Thr Lys Glu Leu Ala 35 40 45

aaa geg tee gta tet egt ate gtt ate gag egt eeg get aag age ate 192 Lys Ala Ser Val Ser Arg Ile Val Ile Glu Arg Pro Ala Lys Ser Ile 50 55

cgt gta acc att cac act gct cgc ccg ggt atc gtt atc ggt aaa aaa 240 Arg Val Thr Ile His Thr Ala Arg Pro Gly Ile Val Ile Gly Lys Lys 65 70 75 80

ggt gaa gac gta gaa aaa ctg cgt aag gtc gta gcg gac atc gct ggc 288 Gly Glu Asp Val Glu Lys Leu Arg Lys Val Val Ala Asp Ile Ala Gly 85 90 95

gtt cct gca cag atc aac atc gcc gaa gtt cgt aag cct gaa ctg gac 336
Val Pro Ala Gln Ile Asn Ile Ala Glu Val Arg Lys Pro Glu Leu Asp
100 105 110

gca aaa ctg gtt gct gac agc atc act tct cag ctg gaa cgt cgc gtt 384 Ala Lys Leu Val Ala Asp Ser Ile Thr Ser Gln Leu Glu Arg Arg Val 115 120 125

atg ttc cgt cgt gct atg aag cgt gct gta cag aac gca atg cgt ctg 432 Met Phe Arg Arg Ala Met Lys Arg Ala Val Gln Asn Ala Met Arg Leu 130 135 140

ggc gct aaa ggt att aaa gtt gaa gtt agc ggc cgt ctg ggc ggc gcg 480 Gly Ala Lys Gly Ile Lys Val Glu Val Ser Gly Arg Leu Gly Gly Ala
145 150 155 160

gaa atc gca cgt acc gaa tgg tac cgc gaa ggt cgc gta ccg ctg cac 528 Glu Ile Ala Arg Thr Glu Trp Tyr Arg Glu Gly Arg Val Pro Leu His 165 170 175

١

PCT/US00/34419 WO 01/48209

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				ggc												624
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	_	_	_	egt Arg			_		taa *							702
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	L> CI	-	. (333									-				
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				acc Thr												144
				tct Ser												192
				ctg Leu												240
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<213> Escherichia coli

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ctt gag tac gat ccg aac cgt tcc gcg aac atc gcg ctg gtt ctg tac 2 Leu Glu Tyr Asp Pro Asn Arg Ser Ala Asn Ile Ala Leu Val Leu Tyr 85 90 95	288
aaa gac ggt gaa cgc cgt tac atc ctg gcc cct aaa ggc ctg aaa gct 3 Lys Asp Gly Glu Arg Arg Tyr Ile Leu Ala Pro Lys Gly Leu Lys Ala 100 105 110	336
ggc gac cag att cag tct ggc gtt gat gct gca atc aaa cca ggt aac 3 Gly Asp Gln Ile Gln Ser Gly Val Asp Ala Ala Ile Lys Pro Gly Asn 115 120 125	884
acc ctg ccg atg cgc aac atc ccg gtt ggt tct act gtt cat aac gta Thr Leu Pro Met Arg Asn Ile Pro Val Gly Ser Thr Val His Asn Val 130 135 140	132
gaa atg aaa cca ggt aaa ggc ggt cag ctg gca cgt tcc gct ggt act Glu Met Lys Pro Gly Lys Gly Gly Gln Leu Ala Arg Ser Ala Gly Thr 145 150 155 160	180
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cgt tct ggt gaa atg cgt aaa gta gaa gca gac tgc cgt gca act ctg 5 Arg Ser Gly Glu Met Arg Lys Val Glu Ala Asp Cys Arg Ala Thr Leu 180 185 190	576
ggc gaa gtt ggc aat gct gag cat atg ctg cgc gtt ctg ggt aaa gca 6 Gly Glu Val Gly Asn Ala Glu His Met Leu Arg Val Leu Gly Lys Ala 195 200 205	524
ggt gct gca cgc tgg cgt ggt gtt cgt ccg acc gtt cgc ggt acc gcg 6 Gly Ala Ala Arg Trp Arg Gly Val Arg Pro Thr Val Arg Gly Thr Ala 210 215 220	572
atg aac ccg gta gac cac cca cat ggt ggt gga ggt cgt aac ttt 7 Met Asn Pro Val Asp His Pro His Gly Gly Glu Gly Arg Asn Phe 225 230 235 240	720
ggt aag cac ccg gta act ccg tgg ggc gtt cag acc aaa ggt aag aag 7 Gly Lys His Pro Val Thr Pro Trp Gly Val Gln Thr Lys Gly Lys Lys 245 250 255	768
acc cgc agc aac aag cgt act gat aaa ttc atc gta cgt cgc cgt agc 8 Thr Arg Ser Asn Lys Arg Thr Asp Lys Phe Ile Val Arg Arg Arg Ser 260 265 270	316
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	gaa Glu															96
	gtt Val	_		_				_	_			_	_		_	144
	ctg Leu 50															192
	aaa Lys															240
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	ggc	_		taa *												303
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)> L> CI 2> (1		. (606	5)												
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	acc Thr															96
	gct Ala															144
	gct Ala 50															192
	ggc Gly															240

Gly Gly V	gtg acc Val Thr													288
aac aag a Asn Lys I														336
gta cgt o														384
ccg aaa a Pro Lys T 130														432
gat gtg o Asp Val I 145														480
gcg cgc a														528
ccg gtt a														576
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<210> 132 <211> 630 <212> DNF <213> Esc <220> <221> CDS <222> (1) <400> 132 atg att g Met Ile G 1 gaa gac g	2 2 3 A Cherich 6 3(63 2 ggt tta Gly Leu ggc gtt Gly Val 20 act cag	gtc Val 5 tct Ser	ggt Gly atc Ile	Lys cca Pro	aaa Lys gta Val	val acc Thr 25 gct	Gly 10 gta Val	Met atc Ile gat	Thr gaa Glu ggc	Arg gtt Val tac	gaa Glu 30	Phe 15 gca Ala gct	Thr aac Asn att	
<210> 132 <211> 630 <212> DNF <213> Esc <220> <221> CDS <222> (1) <400> 132 atg att g Met Ile G 1 gaa gac g Glu Asp G	cherich che	gtc Val 5 tct ser gtt Val	ggt Gly atc Ile aaa Lys	cca pro gac Asp	aaa Lys gta Val ctg Leu 40	acc Thr 25 gct Ala	Gly 10 gta Val aac Asn	Met atc Ile gat Asp	Thr gaa Glu ggc Gly	gtt Val tac Tyr 45	gaa Glu 30 cgt Arg	Phe 15 gca Ala gct Ala cct	Thr aac Asn att Ile	96

65					70				75				80	
						ggc Gly								288
						gac Asp								336
						gca Ala								384
						ggt Gly 135								432
						act Thr								480
						aac Asn								528
_	-	-	-	_	_	gag Glu	-	_	_	_	_		_	576
						agc Ser								624
gcg Ala	taa *													630
<213 <212)> 13 i> 31 ?> DN 3> Es	.2 (A.	richi	ia co	oli									
)> .> CI !> (1		(312	!)										
atg		aac				cgt Arg								48
						gcg Ala								96
						ccg Pro								144

ttc Phe	act Thr 50	gtt Val	ctg Leu	atc Ile	tcc Ser	ccg Pro 55	cac His	gtc Val	aac Asn	aaa Lys	gac Asp 60	gcg Ala	cgc Arg	gat Asp	cag Gln	192
								ctg Leu								240
gag Glu	aaa Lys	acc Thr	gtt Val	gat Asp 85	gct Ala	ctg Leu	atg Met	cgt Arg	ctg Leu 90	gat Asp	ctg Leu	gct Ala	gcc Ala	ggt Gly 95	gta Val	288
_		_		_	ctg Leu											312
<211 <212)> 13 .> 31 !> DN !> Es	L5 VA	richi	ia co	oli											
	.> CI	os L)	. (31	5)					,	•						
atg		cgc						cag Gln								48
gag Glu	tat Tyr	cag Gln	cgt Arg 20	cgg Arg	cat His	aat Asn	ccc Pro	atc Ile 25	tgg Trp	cca Pro	gaa Glu	ctg Leu	gaa Glu 30	gca Ala	gtg Val	96
ctg Leu	aaa Lys	tct Ser 35	cac His	ggt Gly	gcg Ala	cat His	aac Asn 40	tac Tyr	gcc Ala	atc Ile	tat Tyr	ctc Leu 45	gac Asp	aaa Lys	gcg Ala	144
								gag Glu								192
aat Asn 65	gcg Ala	gtt Val	gcc Ala	agc Ser	act Thr 70	gat Asp	gtt Val	Cys Cys	caa Gln	cgt Arg 75	tgg Trp	tgg Trp	aaa Lys	tat Tyr	atg Met 80	240
								gat Asp								288
					tac Tyr											315
<213 <213	0> 13 L> 86 2> DI	54 NA	ri ob	i a	-1 i											

<220> <221> CDS <222> (1)...(864) <400> 135 atg atc ege agt atg acc gee tac gee egg egt gaa atc aag ggt gaa Met Ile Arg Ser Met Thr Ala Tyr Ala Arg Arg Glu Ile Lys Gly Glu tgg ggg agc gca acc tgg gaa atg cgc tcg gta aac cag cgt tat ctg Trp Gly Ser Ala Thr Trp Glu Met Arg Ser Val Asn Gln Arg Tyr Leu 25 gaa act tac ttt cgt ctg ccg gag cag ttc cgt agc ctt gaa cct gtc Glu Thr Tyr Phe Arg Leu Pro Glu Gln Phe Arg Ser Leu Glu Pro Val gtt cgc gag cgt att cgt tct cgc ctg acg cgc ggt aaa gtg gaa tgt 192 Val Arg Glu Arg Ile Arg Ser Arg Leu Thr Arg Gly Lys Val Glu Cys acc ctg cgc tat gag cca gat gtt agc gcg caa ggt gag ctg atc ctc 240 Thr Leu Arg Tyr Glu Pro Asp Val Ser Ala Gln Gly Glu Leu Ile Leu aac gaa aaa ctg gct aaa cag ctg gta act gcc gcg aac tgg gta aaa 288 Asn Glu Lys Leu Ala Lys Gln Leu Val Thr Ala Ala Asn Trp Val Lys 85 90 atg cag agt gac gaa ggg gaa atc aac ccg gtt gat att cta cgc tgg 336 Met Gln Ser Asp Glu Gly Glu Ile Asn Pro Val Asp Ile Leu Arg Trp 100 105 ceg ggc gtg atg gca gcc cag gag cag gat ctt gac gcc att gcc gct 384 Pro Gly Val Met Ala Ala Gln Glu Gln Asp Leu Asp Ala Ile Ala Ala 115 120 gaa att ete geg geg etg gat ggt aeg etg gae gae ttt att gte geg 432 Glu Ile Leu Ala Ala Leu Asp Gly Thr Leu Asp Asp Phe Ile Val Ala ege gaa ace gaa ggt cag gca etg aaa gca ttg ate gag cag egt etg 480 Arg Glu Thr Glu Gly Gln Ala Leu Lys Ala Leu Ile Glu Gln Arg Leu gaa ggc gtc acc gcc gaa gtg gtc aaa gtc cgc tcc cat atg ccg gaa 528 Glu Gly Val Thr Ala Glu Val Val Lys Val Arg Ser His Met Pro Glu atc ctg caa tgg cag cgt gag cgt ctg gtc gcg aag ctg gaa gat gct Ile Leu Gln Trp Gln Arg Glu Arg Leu Val Ala Lys Leu Glu Asp Ala cag gtg caa ctg gaa aac aac cgt ctg gag cag gaa ctg gtt ctg ctg 624 Gln Val Gln Leu Glu Asn Asn Arg Leu Glu Gln Glu Leu Val Leu Leu 200 gca caa cga att gac gtt gcc gaa gaa ctg gat cgc ctc gaa gcg cat Ala Gln Arg Ile Asp Val Ala Glu Glu Leu Asp Arg Leu Glu Ala His

	aaa Lys															720
	ctg Leu															768
	tcg Ser															816
	gtg Val	_			_	_	_		_		_			_	taa *	864
<21:	0> 13 L> 49 2> DI 3> Es	92 NA	rich:	ia co	oli ,		• •									
	0> L> CI 2> (3		. (492	2)	-											
atg	0> 13 agc Ser	aca														48
	caa Gln															96
	ggt Gly															144
_	tac Tyr 50		-	-				-	_	_	_					192
	ttg Leu															240
	tca Ser															288
	aaa Lys		_					_		_	_			_		336
	cgt Arg															384
atg	caa	tgt	ttc	tat	cac	att	att	aac	aat	tgt	gag	gat	gat	agt	gtt	432

Met Gln Cys Phe Tyr His Ile Ile Asn Asn Cys Glu Asp Asp Ser Val aag agt aaa geg cag gea tat att gaa ete tta aac gat aat tea gaa 480 Lys Ser Lys Ala Gln Ala Tyr Ile Glu Leu Leu Asn Asp Asn Ser Glu 150 492 gat aat ggc taa Asp Asn Gly * <210> 137 <211> 1947 <212> DNA <213> Escherichia coli <220> <221> CDS <222> (1) ... (1947) <400> 137 atg aat att tta ggt ttt ttc cag cga ctc ggt agg gcg tta cag ctc Met Asn Ile Leu Gly Phe Phe Gln Arg Leu Gly Arg Ala Leu Gln Leu cet ate geg gtg etg eeg gtg geg gea etg ttg etg ega tte ggt eag 96 Pro Ile Ala Val Leu Pro Val Ala Ala Leu Leu Arg Phe Gly Gln 20 cca gat tta ctt aac gtt gcg ttt att gcc cag gcg ggc ggt gcg att 144 Pro Asp Leu Leu Asn Val Ala Phe Ile Ala Gln Ala Gly Gly Ala Ile 40 ttt gat aac ctc gca tta atc ttc gcc atc ggt gtg gca tcc agc tgg 192 Phe Asp Asn Leu Ala Leu Ile Phe Ala Ile Gly Val Ala Ser Ser Trp 50 55 teg aaa gac age get geg geg geg etg geg get geg gta get tac 240 Ser Lys Asp Ser Ala Gly Ala Ala Ala Leu Ala Gly Ala Val Gly Tyr ttt gtg tta acc aaa gcg atg gtg acc atc aac cca gaa att aac atg 288 Phe Val Leu Thr Lys Ala Met Val Thr Ile Asn Pro Glu Ile Asn Met 85 ggt gta ctg gcg ggt atc att acc ggt ctg gtt ggt ggc gca gcc tat 336 Gly Val Leu Ala Gly Ile Ile Thr Gly Leu Val Gly Gly Ala Ala Tyr 100 105 aac cgt tgg tcc gat att aaa ctg ccg gac ttc ctg agc ttc ttc ggc 384 Asn Arg Trp Ser Asp Ile Lys Leu Pro Asp Phe Leu Ser Phe Phe Gly 115 gge aaa ege ttt gtg eeg att gee ace gga tte tte tge etg gtg etg 432 Gly Lys Arg Phe Val Pro Ile Ala Thr Gly Phe Phe Cys Leu Val Leu 130 135 geg gee att ttt ggt tae gte tgg eeg eeg gta eag eae get ate eat 480 Ala Ala Ile Phe Gly Tyr Val Trp Pro Pro Val Gln His Ala Ile His 145 150 155

gca ggc Ala Gly												528
ttt ggt Phe Gly		Asn A										576
ctg aac Leu Asn		-	_	_			_				_	 624
ggt acg Gly Thr 210	•		_			_			_		_	 672
acc gcg Thr Ala 225			t Ser				_		_	_		 720
ctg ccg Leu Pro												768
cgt ccg Arg Pro		Gly G	_	_			_	_	_			816
ctg acc Leu Thr												864
ccg ctg Pro Leu 290	_		_	Ala	_	_				_	_	912
gtg gca Val Ala 305			y Ile									960
gct atc Ala Ile												1008
gtc tgg Val Trp		Leu Va										1056
gtg gtg Val Val												1104
cgt gaa Arg Glu 370				Ile								1152
act gaa Thr Glu 385			r Gln									1200

				aac Asn 405											1248
				gct Ala											1296
				tct Ser											1344
				gcg Ala											1392
				ggt Gly										ccg Pro 480	1440
				cct Pro 485											1488
				ctg Leu											1536
				gac Asp											1584
				ccg Pro											1632
				atc Ile							_	_	_		1680
_			_	gag Glu 565		_	_		_		_		_		1728
				Gly ggc											1776
				ccg Pro											1824
				atg Met											1872
				atc Ile											1920
aca	ccg	ctg	tat	gaa	atc	aaa	aag	taa							1947

Thr Pro Leu Tyr Glu Ile Lys Lys * 645

<210> 138 <211> 1239 <212> DNA <213> Escherichia coli <220> <221> CDS <222> (1)...(1239) <400> 138 atg aag act atc ttc agg tac att ctt ttt tta gca ctg tat tct tgt 48 Met Lys Thr Ile Phe Arg Tyr Ile Leu Phe Leu Ala Leu Tyr Ser Cys tgt aat aca gtc agt gca tat aca agt ttt att gtg gga aat aat gca Cys Asn Thr Val Ser Ala Tyr Thr Ser Phe Ile Val Gly Asn Asn Ala 20 25 gga gtt gat aac tat cga ggc ccc tcc act gcc gca cag atg acc ttt 144 Gly Val Asp Asn Tyr Arg Gly Pro Ser Thr Ala Ala Gln Met Thr Phe 40 aat tac aca tca aca gca agc aac ttg gtt ttt tat aaa ccc acg cag 192 Asn Tyr Thr Ser Thr Ala Ser Asn Leu Val Phe Tyr Lys Pro Thr Gln 55 50 ctc ggc ccg act ggg gta aaa atg tac tgg tca tac ctg gat aca ggt 240 Leu Gly Pro Thr Gly Val Lys Met Tyr Trp Ser Tyr Leu Asp Thr Gly acc ggt ggt ggt att ctt tac tgc aat aca tct ggc aga gcg aat cct Thr Gly Gly Gly Ile Leu Tyr Cys Asn Thr Ser Gly Arg Ala Asn Pro ggt cca ata act att gaa aat gcc atg gtc tat tca ggt aaa gat tat Gly Pro Ile Thr Ile Glu Asn Ala Met Val Tyr Ser Gly Lys Asp Tyr 100 gge gga cat aaa cta ttt aat aca tet gtt cet ggt etg tat tae ace 384 Gly Gly His Lys Leu Phe Asn Thr Ser Val Pro Gly Leu Tyr Tyr Thr 120 atg tta ata tca agg gtc tgg tct gca tac gat aca ata act gac att 432 Met Leu Ile Ser Arg Val Trp Ser Ala Tyr Asp Thr Ile Thr Asp Ile 130 caa tcg cca gga atc tat atc gga gat cct tcc aac caa gaa ttt ttc 480 Gln Ser Pro Gly Ile Tyr Ile Gly Asp Pro Ser Asn Gln Glu Phe Phe 145 155 150 ttt tcc gtc aca gac agc gat cta caa act aag ggt tgc aac aaa gca 528 Phe Ser Val Thr Asp Ser Asp Leu Gln Thr Lys Gly Cys Asn Lys Ala 165 170 175 gac gac tac gat aag ttt tgg gct att ggt ggt ata gta cac aac ata 576 Asp Asp Tyr Asp Lys Phe Trp Ala Ile Gly Gly Ile Val His Asn Ile 180

					aca Thr											624
					agt Ser											672
					aaa Lys 230											720
					aat Asn											768
					cca Pro											816
					aca Thr											864
					aat Asn											912
					gta Val 310											960
acg Thr	ctt Leu	act Thr	gga Gly	agc Ser 325	act Thr	gcc Ala	gcc Ala	aaa Lys	ggc 330	gtt Val	ggc Gly	gta Val	ctc Leu	att Ile 335	gaa Glu	1008
					aaa Lys											1056
					ata Ile											1104
					caa Gln											1152
					caa Gln 390											1200
		_		_	act Thr		_	_				_				1239

<210> 139

<211> 597 <212> DNA

<213> Escherichia coli <220> <221> CDS <222> (1) ... (597) <400> 139 atg cat ccc act caa cgt aag ctg atg aag aga ata att ctg ttt ctg Met His Pro Thr Gln Arg Lys Leu Met Lys Arg Ile Ile Leu Phe Leu tca tta ctg ttt tgc atc gcc tgt cca gcc att gct gga cag gat att 96 Ser Leu Leu Phe Cys Ile Ala Cys Pro Ala Ile Ala Gly Gln Asp Ile gac ctt gtt gcc aat gta aaa aac agc acc tgc aaa agc gga atc agt 144 Asp Leu Val Ala Asn Val Lys Asn Ser Thr Cys Lys Ser Gly Ile Ser aac cag ggt aat att gat ctt ggc gtc gtt ggg gtg gga tat ttt tca 192 Asn Gln Gly Asn Ile Asp Leu Gly Val Val Gly Val Gly Tyr Phe Ser 55 ggt aat gtt act cct gaa agt tat caa cca ggt gga aaa gag ttc act 240 Gly Asn Val Thr Pro Glu Ser Tyr Gln Pro Gly Gly Lys Glu Phe Thr 70 atc act gta tcc gac tgt gca tta cag gga act ggc gat gtg cta aat 288 Ile Thr Val Ser Asp Cys Ala Leu Gln Gly Thr Gly Asp Val Leu Asn 90 cag tta cat att gat ttt aga gcc ctt agc ggt gtc atg gct gct ggc 336 Gln Leu His Ile Asp Phe Arg Ala Leu Ser Gly Val Met Ala Ala Gly tct agg caa ata ttt gct aat gaa att tcg tca gga gca agt aat gta 384 Ser Arg Gln Ile Phe Ala Asn Glu Ile Ser Ser Gly Ala Ser Asn Val 120 gga gta gtt ata ttt tct act cag gat tcg gcg aat aca ttc aat gtt 432 Gly Val Val Ile Phe Ser Thr Gln Asp Ser Ala Asn Thr Phe Asn Val ctt aat get tea gge gga tet egt tee gtt tat eea gta atg teg gat Leu Asn Ala Ser Gly Gly Ser Arg Ser Val Tyr Pro Val Met Ser Asp gac atg aat ggt tca tcc tgg aaa ttt agc acc cga atg caa aaa atc 528 Asp Met Asn Gly Ser Ser Trp Lys Phe Ser Thr Arg Met Gln Lys Ile gat cet gea ttg agt gtt aca tet ggt caa ett atg age cat gtg tta 576 Asp Pro Ala Leu Ser Val Thr Ser Gly Gln Leu Met Ser His Val Leu 185 597 gtg gat att tac tac gaa taa

<210> 140

Val Asp Ile Tyr Tyr Glu *

195

<211> 606 <212> DNA <213> Escherichia coli <220> <221> CDS <222> (1) ... (606) <400> 140 atg atg aca ttt aaa aat tta cgt tat gga tta tcc agc agt gtc gtt Met Met Thr Phe Lys Asn Leu Arg Tyr Gly Leu Ser Ser Val Val ttg get gee tea ttg tte age gta ete tet tat geg gea aca gae agt Leu Ala Ala Ser Leu Phe Ser Val Leu Ser Tyr Ala Ala Thr Asp Ser att gga ctg acc gtt att act act gta gaa atg ggt act tgt acc gct 144 Ile Gly Leu Thr Val Ile Thr Thr Val Glu Met Gly Thr Cys Thr Ala aca tta gta aat gac tct gat cag gac att tct gtt gtt gat ttt ggt 192 Thr Leu Val Asn Asp Ser Asp Gln Asp Ile Ser Val Val Asp Phe Gly 55 gat gta tat att tct gaa atc aat gcc aag acc aaa gta aaa aca ttc Asp Val Tyr Ile Ser Glu Ile Asn Ala Lys Thr Lys Val Lys Thr Phe 70 75 aaa ctc aaa ttc aaa gac tgt gcg ggt atc ccc aat aaa aaa gcg caa 288 Lys Leu Lys Phe Lys Asp Cys Ala Gly Ile Pro Asn Lys Lys Ala Gln 85 90 ata aaa tta acc aag cga gcc aca tgc gag gga act gct aat gac ggt 336 Ile Lys Leu Thr Lys Arg Ala Thr Cys Glu Gly Thr Ala Asn Asp Gly gcg ggg ttt gca aat ggt tcc aca gcc gca gat aaa gca agt gct gtc 384 Ala Gly Phe Ala Asn Gly Ser Thr Ala Ala Asp Lys Ala Ser Ala Val 120 gcc gtt gaa gtc tgg agc act gta act ccg gca aca ggg agt gca aca 432 Ala Val Glu Val Trp Ser Thr Val Thr Pro Ala Thr Gly Ser Ala Thr caa ttt agc tgt gta aca cca gca tca caa gag gta aca atc tcc act Gln Phe Ser Cys Val Thr Pro Ala Ser Gln Glu Val Thr Ile Ser Thr 150 gca gcc aat gcg gtc gtt tat tat ccg atg agt gca cgc ctg gtc gtg Ala Ala Asn Ala Val Val Tyr Tyr Pro Met Ser Ala Arg Leu Val Val gaa aaa aat aaa acc gta aac aat gtc act gcg ggt aag ttt tct gca Glu Lys Asn Lys Thr Val Asn Asn Val Thr Ala Gly Lys Phe Ser Ala 180 cca gcc aca ttt aca gta acc tat aac taa 606 Pro Ala Thr Phe Thr Val Thr Tyr Asn *

<213 <212)> 14 l> 61 l> DN l> Es	.2 TA	ichi	ia co	oli									
	.> CI		(612	2)										
atg	_	ttc		_	_	ttc Phe	_			_	 -		_	48
		_				ata Ile			_	_				96
						gat Asp								144
						atc Ile 55								192
						aca Thr								240
						aca Thr								288
						ggc Gly								336
		_			_	tca Ser		_			-	_		 384
						agt Ser 135								432
						ttc Phe								480
						atg Met								528
						gat Asp								576
						aat Asn								612

195 , 200 <210> 142 <211> 420 <212> DNA <213> Escherichia coli <220> <221> CDS <222> (1)...(420) <400> 142 atg gca atg act tac cac ctg gac gtc gtc agc gca gag caa caa atg Met Ala Met Thr Tyr His Leu Asp Val Val Ser Ala Glu Gln Met ttc tct ggt ctg gtc gag aaa atc cag gta acg ggt agc gaa ggt gaa Phe Ser Gly Leu Val Glu Lys Ile Gln Val Thr Gly Ser Glu Gly Glu ctg ggg atc tac cct ggc cac gca ccg ctg ctc acc gcc att aag cct 144 Leu Gly Ile Tyr Pro Gly His Ala Pro Leu Leu Thr Ala Ile Lys Pro ggt atg att cgc atc gtg aaa cag cac ggt cac gaa gag ttt atc tat 192 Gly Met. Ile Arg Ile Val Lys Gln His Gly His Glu Glu Phe Ile Tyr ctg tct ggc ggc att ctt gaa gtg cag cct ggc aac gtg acc gtt ctg 240 Leu Ser Gly Gly Ile Leu Glu Val Gln Pro Gly Asn Val Thr Val Leu gee gae ace gea att ege gge eag gat ete gae gaa geg ega gee atg 288 Ala Asp Thr Ala Ile Arg Gly Gln Asp Leu Asp Glu Ala Arg Ala Met gaa geg aaa egt aag get gaa gag eac att age age tet eac gge gae 336 Glu Ala Lys Arg Lys Ala Glu Glu His Ile Ser Ser His Gly Asp 105 gta gat tac gct cag gcg tct gcg gaa ctg gcc aaa gcg atc gcg cag 384 Val Asp Tyr Ala Gln Ala Ser Ala Glu Leu Ala Lys Ala Ile Ala Gln 120 ctg cgc gtt atc gag ttg acc aaa aaa gcg atg taa 420 Leu Arg Val Ile Glu Leu Thr Lys Lys Ala Met * . 130

<210> 143
<211> 1383
<212> DNA
<213> Escherichia coli
<220>
<221> CDS
<222> (1) ... (1383)
<400> 143

atg gct act gga aag att gtc cag gta atc ggc gcc gta gtt gac gtc 48

Met :	Ala	Thr	Gly	Lys 5	Ile	Val	Gln	Val	Ile 10	Gly	Ala	Val	Val	Asp 15	Val	
gaa Glu																96
caa Gln																144
ggc																192
cgc Arg 65		_	_	_		_		_		_		_	-	_	_	240
ggt		_		_		_		_		_	-		_	_	_	288
gac Asp																336
gca Ala																384
				gtt Val												432
aaa Lys 145																480
atg Met				_					-							528
ttt Phe	_		_	ggt Gly	_	_		_				_				576
gaa Glu	_		_	tcc Ser		_		_		_		_				624
Gln				ccg Pro												672
GIn	Met 210 acc	Asn atg	Glu		Pro	Gly 215 ttc	Asn egt	Arg gac	Leu gaa	Arg ggt	Val 220 cgt	Ala gac	Leu	Thr	Gly ctg	720

245 250 255 gea etg etg gge egt atg eet tea geg gta ggt tat eag eeg ace etg 816 Ala Leu Leu Gly Arg Met Pro Ser Ala Val Gly Tyr Gln Pro Thr Leu 265 geg gaa gag atg ggc gtt etg eag gaa egt ate ace tee ace aaa act 864 Ala Glu Glu Met Gly Val Leu Gln Glu Arg Ile Thr Ser Thr Lys Thr 280 ggt tet ate ace tee gta cag gea gta tae gta cet geg gat gae ttg 912 Gly Ser Ile Thr Ser Val Gln Ala Val Tyr Val Pro Ala Asp Asp Leu 290 295 act gac eeg tet eeg gea ace ace ttt geg cac ett gac gea ace gtg .960 Thr Asp Pro Ser Pro Ala Thr Thr Phe Ala His Leu Asp Ala Thr Val 305 310 gta ctg agc cgt cag atc gcg tct ctg ggt atc tac ccg gcc gtt gac 1008 Val Leu Ser Arg Gln Ile Ala Ser Leu Gly Ile Tyr Pro Ala Val Asp 325 330 eeg etg gae tee aee age egt eag etg gae eeg etg gtg gtt ggt eag 1056 Pro Leu Asp Ser Thr Ser Arg Gln Leu Asp Pro Leu Val Val Gly Gln 340 345 gaa cac tac gac acc gcg cgt ggc gtt cag tcc atc ctg caa cgt tat 1104 Glu His Tyr Asp Thr Ala Arg Gly Val Gln Ser Ile Leu Gln Arg Tyr 355 360 cag gaa ctg aaa gac atc atc gcc atc ctg ggt atg gat gaa ctg tct 1152 Gln Glu Leu Lys Asp Ile Ile Ala Ile Leu Gly Met Asp Glu Leu Ser 370 gaa gac aaa ctg gtg gta gcg cgt gct cgt aag atc cag cgc ttc 1200 Glu Glu Asp Lys Leu Val Val Ala Arg Ala Arg Lys Ile Gln Arg Phe ctg tcc cag ccg ttc ttc gtg gca gaa gta ttc acc ggt tct ccg ggt Leu Ser Gln Pro Phe Phe Val Ala Glu Val Phe Thr Gly Ser Pro Gly 405 410 aaa tac gtc tcc ctg aaa gac acc atc cgt ggc ttt aaa ggc atc atg 1296 Lys Tyr Val Ser Leu Lys Asp Thr Ile Arg Gly Phe Lys Gly Ile Met 420 425 gaa ggc gaa tac gat cac ctg ccg gag cag gcg ttc tac atg gtc ggt 1344 Glu Gly Glu Tyr Asp His Leu Pro Glu Gln Ala Phe Tyr Met Val Gly 435 440 tcc atc gaa gaa gct gtg gaa aaa gcc aaa aaa ctt taa 1383 Ser Ile Glu Glu Ala Val Glu Lys Ala Lys Lys Leu *

<210> 144

450

<211> 864

<212> DNA

<213> Escherichia coli

<220>

<221> CDS

210

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720

Glu Pro Asp Pro Lys Ala Leu Leu Asp Thr Leu Leu Arg Arg Tyr Val

gaa tot cag gtt tat cag ggc gtg gtt gaa aac ctg gcc agc gag cag

Glu 225	Ser	Gln	Val	Tyr	Gln 230	Gly	Val	Val	Glu	Asn 235	Leu	Ala	Ser	Glu	Gln 240	
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				ggc Gly 85												288
				cgt Arg												336
				ggt Gly												384
				gct Ala												432

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				gaa Glu 165												528
				gat Asp												576
				gct Ala												624
				gaa Glu												672
				tct Ser												720
				atg Met 245												768
				gat Asp								Ala				816
				ctc Leu												864
_	_			ctc Leu			_	_	_		_	-	-	_	_	912
				gtt Val												960
				acc Thr 325												1008
				gtt Val												1056
				acc Thr												1104
				tcc Ser												1152

	_			ctg Leu					_		_	-	_	_		1200
_	_	_	_	gcg Ala 405			_		_		_		_	_	-	1248
	_	_	_	ctt Leu	_			_				Ğlu	_	_		1296
_		-		gcg Ala	-	-		-		_	_		_	_	_	1344
				cgt Arg												1392
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Ser	Gly 50	Ala	Leu	Ala	Pro	Glu 55	Thr	Leu	Ala	Glu	Ser 60	Phe	Ile	Ala	Val	
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gct Ala	gaa Glu	aat Asn	ggt Gly	cgt Arg 85	ctt Leu	aac Asn	gcg Ala	ctc Leu	ccg Pro 90	gat Asp	gtt Val	ctg Leu	gag Glu	cag Gln 95	ttt Phe	288
att Ile	cac His	ctg Leu	cgt Arg 100	gcc Ala	gtg Val	agt Ser	gag Glu	gct Ala 105	acc Thr	gct Ala	gag Glu	gta Val	gac Asp 110	gtc Val	att Ile	336
			gca Ala													384
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tct Ser	taa *															534
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			cgt Arg													144
			aag Lys													192

ctg Leu					Ala					Ile					Asn	240
65					70					75		•			80	
aaa Lys																288
gaa Glu																336
cgt Arg																384
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	aat	act	cag	ttc												192
ctg Leu				Phe	Phe	55	Val	1466	GLY	neu	60					
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aat aac ctt cag ctg gac ctg cgt aca ttc tcg ctg gtg gat cca caa 96
Asn Asn Leu Gln Leu Asp Leu Arg Thr Phe Ser Leu Val Asp Pro Gln
20 25 30

aac ccc cca gcc acc ttc tgg aca atc aat att gac tcc atg ttc ttc 144
Asn Pro Pro Ala Thr Phe Trp Thr Ile Asn Ile Asp Ser Met Phe Phe
35 40 45

tcg gtg gtg ctg ggt ctg ttg ttc ctg gtt tta ttc cgt agc gta gcc 192 Ser Val Val Leu Gly Leu Leu Phe Leu Val Leu Phe Arg Ser Val Ala

aaa aag gcg acc agc ggt gtg cca ggt aag ttt cag acc gcg att gag 240 Lys Lys Ala Thr Ser Gly Val Pro Gly Lys Phe Gln Thr Ala Ile Glu 65 70 75 80

ctg gtg atc ggc ttt gtt aat ggt agc gtg aaa gac atg tac cat ggc 288 Leu Val Ile Gly Phe Val Asn Gly Ser Val Lys Asp Met Tyr His Gly 85 90 95

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ttc ctg atg aac ctg atg gat tta ctg cct atc gac ctg ctg ccg tac 384
Phe Leu Met Asn Leu Met Asp Leu Leu Pro Ile Asp Leu Leu Pro Tyr
115 120 125

att gct gaa cat gta ctg ggt ctg cct gca ctg cgt gtg gtt ccg tct 432

Ile Ala Glu His Val Leu Gly Leu Pro Ala Leu Arg Val Val Pro Ser

130 135 140

gcg gac gtg aac gta acg ctg tct atg gca ctg ggc gta ttt atc ctg 480 Ala Asp Val Asn Val Thr Leu Ser Met Ala Leu Gly Val Phe Ile Leu 145 150 155

att ctg ttc tac agc atc aaa atg aaa ggc atc ggc ggc ttc acg aaa 528

Ile Leu Phe Tyr Ser Ile Lys Met Lys Gly Ile Gly Gly Phe Thr Lys
165 170 175

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tta atc ctt gaa ggg gta agc ctg ctg tcc aaa cca gtt tca ctc ggt
Leu Ile Leu Glu Gly Val Ser Leu Leu Ser Lys Pro Val Ser Leu Gly
195
200
205

ttg cga ctg ttc ggt aac atg tat gcc ggt gag ctg att ttc att ctg 672 Leu Arg Leu Phe Gly Asn Met Tyr Ala Gly Glu Leu Ile Phe Ile Leu

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	agc Ser															144
_	gca Ala 50	_		_			_	_		_			_	~~	-	192
	cag Gln															240
ttt Phe	ggc Gly	gaa Glu	gct Ala	ttc Phe 85	aaa Lys	gtt Val	ctg Leu	gcg Ala	atg Met 90	ttg Leu	gtg Val	tta Leu	ctg Leu	gtg Val 95	gtg Val	288
	ttg Leu															336
	ttg Leu					Gln										384
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		cgt Arg														192
		tgt Cys														240
	_	gat Asp	_						_	-			-			288
		ttt Phe														336
		atg Met 115														384
		tcg Ser														432
	-	cca Pro	_					_	_		_	_	_			480
		aag Lys														528
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tat	ctg	aag	att	gcc	ccg	gaa	cat	acc	gaa	gaa	aaa	ccg	tta	tcg	aag	624

Tyr	Leu	Lys 195	Ile	Ala	Pro	Glu	His 200	Thr	Glu	Glu	Gly	Pro 205	Leu	Ser	Lys	
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_					cag Gln 230	_				_		_				720
					ccc Pro		_	_	_	_	_	_			_	768
	_		_		aag Lys		_		_		_	_	_	_		816
					ctg Leu											864
		_	_		aag Lys				_	-	-	_	_		_	912
_	_		-		cag Gln 310	_	_	_				_	_	-		960
	_	_	_		tgg Trp	_			_	_	_	_	_		_	1008
					att Ile											1056
					atg Met											1104
_	_		_	_	aaa Lys		_	_	-			_	_	-	_	1152
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	ctt Leu															768
	gat Asp															816
gaa Glu	gcc Ala	aaa Lys 275	gcc Ala	gta Val	acc Thr	gtg Val	cag Gln 280	cca Pro	ccg Pro	cgc Arg	ccg Pro	aaa Lys 285	ccg Pro	tgg Trp	gaa Glu	864
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Phe	Leu	Pro	Val	Ala 85	Ala	Lys	Gln	Leu	Met 90	Ala	Met	Val	Leu	Gly 95	Gly	
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				cag Gln												384
				att Ile												432
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				caa Gln 165												528
•				gta Val			_		_	_				_		576
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				tgc Cys												96
				acg Thr												144

				gcc Ala												192
				ctg Leu												240
				gtg Val 85												288
				cgg Arg												336
				ctg Leu												384
				ctc Leu												432
				gcg Ala												480
			_	gac Asp 165	_	_				_		_	_		_	528
				cag Gln												576
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	gaa Glu															144
	att Ile 50															192
	tgg Trp															240
_	atg Met		-						_		_			_	_	288
att Ile	gat Asp	gat Asp	tac Tyr 100	tac Tyr	gaa Glu	cct Pro	ttc Phe	acc Thr 105	ttc Phe	gac Asp	tac Tyr	gaa Glu	cat His 110	ttg Leu	cat His	336
	gca Ala															384
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	acc Thr															624
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	tgt	_								tgg Trp						720
225	Cys	110	-7-	пур	230		~2~			235	-		-	•	240	

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490

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485

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gca agt tac tcc Ala Ser Tyr Ser 100					336
ctc att cgt aaa Leu Ile Arg Lys . 115					384
cac agc gat ccg His Ser Asp Pro					432
aag tgc ctg agc Lys Cys Leu Ser 145				_	480
tcc aac tgg cag	gaa cta aac	cag ctg att	gcc gcc gct	aac gtc tgg	528

Ser	Asn	Trp	Gln	Glu 165	Leu	Asn	Gln	Leu	Ile 170	Ala	Ala ·	Ala	Asn	Val 175	Trp	
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_	gcg Ala	_	_	_	-			_	_		_	_		_	_	624
	ctt Leu 210															672
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	aaa Lys															864
	aaa Lys 290															912
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	ccg Pro															1056
	ely aaa															1104
	aac Asn 370															1152
	gta Val															1200
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405 410 415

			caa Gln											1296
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			gtg Val 470											1440
			ggg											1488
			tac Tyr											1536
			att Ile											1584
_		_	Gly 999	_	_	_					_		_	1632
			atg Met 550											1680
		_	 tgt Cys	_			_					~		1728
			aaa Lys											1776
			tgg Trp											1824
			cat His											1872
			tca Ser 630											1920
			aac Asn											1968

					gly 333											2016
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					atg Met											2112
	_	_		_	ttt Phe 710	_		_			_					2160
					tat Tyr	_	_	-		-	_			_	_	2208
					gaa Glu											2256
					act Thr											2304
					cgc Arg											2352
_	_			_	acc Thr 790					_	_	_			_	2400
					att Ile											2448
	~	Ser	-	Ser	gac Asp	Trp	Glu		Tyr			Ile	-	Lys	_	2496
					gtg Val											2544
					cat His											2592
					ege Arg 870											2640
					gtg Val											2688

gaa cgc ttt acc Glu Arg Phe Thr 900				y Asn Gly
ggt aaa ggg att Gly Lys Gly Ile 915				
aaa ctc aat tac Lys Leu Asn Tyr 930				
att gac acc gcc Ile Asp Thr Ala 945				
gaa acc aac ggt Glu Thr Asn Gly				
atc acc ggg cgc Ile Thr Gly Arg 980				ı Asp Glu
aag att cgc ttt Lys Ile Arg Phe 995	Arg Asp Ile	Gln Ala Gln 1000	Pro Arg Lys Ilo 1005	e Ile Ser
agc ccc acc tgg Ser Pro Thr Trp 1010		Glu Ser Asp		
gga tac acc aac Gly Tyr Thr Asn 1025	Val His Glu 1030	Leu Ile Pro	Trp Arg Thr Let 1035	ser Gly 1040
cgc cag cag ctc Arg Gln Gln Leu			Met Arg Ala Pho	
agc ctg gtg gct Ser Leu Val Ala 106	Tyr Arg Pro			l Ser Glu
atg cgc cag ata Met Arg Gln Ile 1075				
ctg acg ccg cac Leu Thr Pro His 1090		Gly Ile His		
ctg cta atg ctg Leu Leu Met Leu 1105				
gaa aca gat gcc Glu Thr Asp Ala			Asp Asn Asp Tr	
gta ttc aac gcc	220 000 000	ctg act gcc	cgc gcg gtg gt	c agc caa 3456

Val Phe Asn Ala Asn Gly Ala Leu Thr Ala Arg Ala Val Val Ser Gln cgt gta ccg ccg ggc atg acc atg atg tat cac gcc cag gaa cgc att 3504 Arg Val Pro Pro Gly Met Thr Met Met Tyr His Ala Gln Glu Arg Ile atg aat att cet ggt teg gaa gta act gge atg ege gge gge att cat 3552 Met Asn Ile Pro Gly Ser Glu Val Thr Gly Met Arg Gly Gly Ile His 1175 aac teg gtt acc ege gtt tge eeg aaa eea acg cat atg att gge ggt 3600 Asn Ser Val Thr Arg Val Cys Pro Lys Pro Thr His Met Ile Gly Gly 1195 tac geg cag ctg gec tgg ggc ttt aac tac tac ggc acc gtc gga tcg 3648 Tyr Ala Gln Leu Ala Trp Gly Phe Asn Tyr Tyr Gly Thr Val Gly Ser 1205 aac ege gat gag tte ate atg ate ege aag atg aag aac gtt aac tgg 3696 Asn Arg Asp Glu Phe Ile Met Ile Arg Lys Met Lys Asn Val Asn Trp 1220 1225 ctg gat gat gaa ggt cgc gat cag gta cag gag gcg aaa aaa tga 3741 Leu Asp Asp Glu Gly Arg Asp Gln Val Gln Glu Ala Lys Lys * 1235 1240 <210> 157 <211> 498 <212> DNA <213> Escherichia coli <220> <221> CDS <222> (1)...(498) atg gat ttg tca cag cta aca cca cgt cgt ccc tat ctg ctg cgt gca Met Asp Leu Ser Gln Leu Thr Pro Arg Arg Pro Tyr Leu Leu Arg Ala ttc tat gag tgg ttg ctg gat aac cag ctc acg ccg cac ctg gtg gtg Phe Tyr Glu Trp Leu Leu Asp Asn Gln Leu Thr Pro His Leu Val Val 20 gat gtg acg ctc cct ggc gtg cag gtt cct atg gaa tat gcg cgt gac 144 Asp Val Thr Leu Pro Gly Val Gln Val Pro Met Glu Tyr Ala Arg Asp ggg caa atc gta ctc aac att gcg ccg cgt gct gtc ggc aat ctg gaa 192 Gly Gln Ile Val Leu Asn Ile Ala Pro Arg Ala Val Gly Asn Leu Glu 240 ctg gcg aat gat gag gtg cgc ttt aac gcg cgc ttt ggt ggc att ccg Leu Ala Asn Asp Glu Val Arg Phe Asn Ala Arg Phe Gly Gly Ile Pro cgt cag gtt tct gtg ccg ctg gct gcc gtg ctg gct atc tac gcc cgt 288 Arg Gln Val Ser Val Pro Leu Ala Ala Val Leu Ala Ile Tyr Ala Arg

95 85 90 gaa aat ggc gca ggc acg atg ttt gag cct gaa gct gcc tac gat gaa 336 Glu Asn Gly Ala Gly Thr Met Phe Glu Pro Glu Ala Ala Tyr Asp Glu 100 105 gat acc agc atc atg aat gat gaa gag gca tcg gca gac aac gaa acc 384 Asp Thr Ser Ile Met Asn Asp Glu Glu Ala Ser Ala Asp Asn Glu Thr 120 115 gtt atg tcg gtt att gat ggc gac aag cca gat cac gat gat gac act 432 Val Met Ser Val Ile Asp Gly Asp Lys Pro Asp His Asp Asp Asp Thr 130 135 cat cct gac gat gaa cct ccg cag cca cca cgc ggt ggt cga ccg gca 480 His Pro Asp Asp Glu Pro Pro Gln Pro Pro Arg Gly Gly Arg Pro Ala 145 150 155 tta cgc gtt gtg aag taa 498 Leu Arg Val Val Lys * 165 <210> 158 <211> 639 <212> DNA <213> Escherichia coli <220> <221> CDS <222> (1) ... (639) <400> 158 atg gct gcc gcc aac aaa cgt tcg gta atg acg ctg ttt tcc ggt Met Ala Val Ala Ala Asn Lys Arg Ser Val Met Thr Leu Phe Ser Gly cct act gac atc tat agc cat cag gtc cgc att gtg ctg gct gag aaa 96 Pro Thr Asp Ile Tyr Ser His Gln Val Arg Ile Val Leu Ala Glu Lys 20 ggt gta agt ttc gag atc gaa cac gtg gaa aag gac aat ccg cct cag 144 Gly Val Ser Phe Glu Ile Glu His Val Glu Lys Asp Asn Pro Pro Gln gat ctg att gac ctc aac ecg aat cag age gtt ecg acc etg gtg gat Asp Leu Ile Asp Leu Asn Pro Asn Gln Ser Val Pro Thr Leu Val Asp 50 55 cgt gag ctg acc ctg tgg gaa tct cgc atc att atg gaa tat ctg gat Arg Glu Leu Thr Leu Trp Glu Ser Arg Ile Ile Met Glu Tyr Leu Asp 65 70 gag egt tte eeg cat eeg eea etg atg eet gtt tac eeg gta get ege 288 Glu Arg Phe Pro His Pro Pro Leu Met Pro Val Tyr Pro Val Ala Arg 85

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100

ctg atg Leu Met															384
cgt aag Arg Lys 130															432
cag aag Gln Lys 145															480
ctt gct Leu Ala															528
ggc ccg Gly Pro					_				_		-	_		-	576
cgt gac Arg Asp															624
ctg ggc Leu Gly 210		_	taa *												639
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. 85 90 95

			85				90			95		
			cgt Arg									336
			gac Asp									384
			acc Thr									432
			gca Ala									480
			gcg Ala 165									528
			ege Arg									576
			ttc Phe									624
			gtg Val									672
			gcg Ala	_	_	_	_	_	_		_	720
			aag Lys 245									768
	_		aac Asn		_					 		816
			atg Met									864
			ctg Leu									912
			acg Thr									960
			gaa Glu 325									1008

ege o																1056
gca a Ala 1																1104
ggc c																1152
att o Ile 0 385	_	_					_		_	_	_	_		_	_	1200
gcg c	_	_		-	-		_	_			-	_				1248
ttc a																1296
gcg g Ala G	_		_			-			-	_	-	_			_	1344
gca g Ala G		_	_	-		_			_	_	_		_		_	1392
ctg g Leu G 465	-				_	_		_		_					_	1440
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Arg	Ser	Asp	Val 20	Leu	Arg	Gly	Tyr	Leu 25	Asp	Tyr	Asp	Ala	Lys 30	Lys	Glu	
				gta Val												144
				gca Ala												192
_	_	_	_	acc Thr		_				-						240
		_	_	gaa Glu 85	_	_	_	_	_	_	_	_	_			288
	_	_	_	gct Ala	_		_		_	_	_		_		_	336
			_	cgt Arg	_				_		_	_	_	_	_	384
		_		cag Gln						_	_	-	_	_		432
				gag Glu												480
				atc Ile 165												528
		Val		atc Ile												576
				Gly												624
				cgc Arg												672
				gat Asp												720
				cgc Arg 245												768
				gtg Val												816

260 265 270 cag tgc cag aac gac cgt tcc cag cac aag aac aaa gat cag gcc atg Gln Cys Gln Asn Asp Arg Ser Gln His Lys Asn Lys Asp Gln Ala Met 280 285 aag cag atg aaa gcg aag ctt tat gaa ctg gag atg cag aag aaa aat 912 Lys Gln Met Lys Ala Lys Leu Tyr Glu Leu Glu Met Gln Lys Lys Asn 290 gee gag aaa cag geg atg gaa gat aac aaa tee gac ate gge tgg gge 960 Ala Glu Lys Gln Ala Met Glu Asp Asn Lys Ser Asp Ile Gly Trp Gly 310 age cag att cgt tet tat gte ett gat gae tee ege att aaa gat etg 1008 Ser Gln Ile Arg Ser Tyr Val Leu Asp Asp Ser Arg Ile Lys Asp Leu cgc acc ggg gta gaa acc cgc aac acg cag gcc gtg ctg gac ggc agc 1056 Arg Thr Gly Val Glu Thr Arg Asn Thr Gln Ala Val Leu Asp Gly Ser 340 345 ctg gat caa ttt atc gaa gca agt ttg aaa gca ggg tta tga 1098 Leu Asp Gln Phe Ile Glu Ala Ser Leu Lys Ala Gly Leu * 355 360 <210> 161 <211> 1734 <212> DNA <213> Escherichia coli <220> <221> CDS <222> (1)...(1734) <400> 161 gtg aaa caa cag ata caa ctt cgt cgc cgt gaa gtc gat gaa acg gca 48 Met Lys Gln Gln Ile Gln Leu Arg Arg Glu Val Asp Glu Thr Ala gac ttg ccc gct gaa ttg cct ccc ttg ctg cgc cgt tta tac gcc aqc Asp Leu Pro Ala Glu Leu Pro Pro Leu Leu Arg Arg Leu Tyr Ala Ser cgg gga gta cgc agt gcg caa gaa ctg gaa cgc agt gtt aaa ggt atg Arg Gly Val Arg Ser Ala Gln Glu Leu Glu Arg Ser Val Lys Gly Met ctg ccc tgg cag caa ctg agc ggc gtc gaa aag gcc gtt gag atc ctt 192 Leu Pro Trp Gln Gln Leu Ser Gly Val Glu Lys Ala Val Glu Ile Leu 50 55 tac aac gct ttt cgc gaa gga acg cgg att att gtg gtc ggt gat ttc 240 Tyr Asn Ala Phe Arg Glu Gly Thr Arg Ile Ile Val Val Gly Asp Phe 65 70 gac gcc gac ggc gcg acc agc acg gct cta agc gtg ctg gcg atg cgc 288 Asp Ala Asp Gly Ala Thr Ser Thr Ala Leu Ser Val Leu Ala Met Arg

90

85

					aat Asn											336
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ggc	gcg Ala 130	cag Gln	tta Leu	att Ile	gtc Val	acg Thr 135	gtg Val	gat Asp	aac Asn	ggt Gly	att Ile 140	tcc Ser	tcc Ser	cat His	gcg Ala	432
					cgc Arg 150											480
					gac Asp											528
					tgt Cys											576
ggt Gly	gtg Val	gcg Ala 195	ttt Phe	tat Tyr	ctg Leu	atg Met	ctg Leu 200	gcg Ala	ctg Leu	cgc Arg	acc Thr	ttt Phe 205	ttg Leu	cgc Arg	gat Asp	624
					gag Glu											672
					gcg Ala 230											720
					att Ile											768
					ccg Pro											816
					ctc Leu											864
					gcc Ala											912
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					aac Asn											1008

			ctg Leu												1056
			Gly ggg												1104
_	_		ctg Leu	_	_	_			-	_			_	_	1152
_			gcg Ala		_		_		_	-					1200
_		_	999 Gly 405	_		_	_	_		_	_	_		_	1248
			ggc Gly												1296
			ctg Leu												1344
			gtt Val												1392
			gac Asp												1440
			ctg Leu 485												1488
			gac Asp			Phe									1536
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	Gln Leu Gl		act ccg gca Thr Pro Ala		
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-	Met Val Gli		cac ege ggg His Arg Gly		
			tta ctg gca Leu Leu Ala 60		
		Ser Ser Ala	cgt ttg ctg Arg Leu Leu 75		
			aag ttt cgt Lys Phe Arg 90		
	•	-	ccc cag cgt Pro Gln Arg	_	_
			tta cag gca Leu Gln Ala		-
		_	atg ctt gaa Met Leu Glu 140		_
acc ggg ctg	cgt gtc tct	gaa ctg gtc	gga ctg aca	atg agt gat	atc 480

Thr 145	Gly	Leu	Arg	Val	Ser 150	Glu	Leu	Val	Gly	Leu 155	Thr	Met	Ser	Asp	Ile 160	
ago Ser	ctg Leu	cgt Arg	cag Gln	ggc Gly 165	gtg Val	gta Val	cgg Arg	gtc Val	att Ile 170	ggt Gly	aaa Lys	ggc	aac Asn	aaa Lys 175	gag Glu	528
_	ctg Leu		_			_			_			_	-			576
_	gaa Glu			-	_		_	_						_		624
	ttt Phe 210															672
	cgt Arg															720
	tca Ser															768
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	tcc Ser		_				_		_	_			_	_		864
	ctt Leu 290			_			_			tga *						897
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	ggc															96
	cag Gln															144

_	_				_	_	gga Gly	_			_			_	_	192
							aaa Lys									240
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							acc Thr									336
_		_		_	_	_	acc Thr 120	_	_		_		_			384
	_	_	_				aac Asn	_	_	_	_	_	_			432
_	-		_		_		ctt Leu			_						480
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							cag Gln									576
							gcg Ala 200									624
Leu		Thr			Met		acc Thr		Leu		Ala	Ala				672
							att Ile									720
							ggc Gly									768
							aac Asn									816
							gta Val 280									864

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ggc Gly 305	aat Asn	ttc Phe	tcg Ser	cgt Arg	ggt Gly 310	gaa Glu	gtc Val	atc Ile	cgc Arg	att Ile 315	tgc Cys	aac Asn	ctc Leu	gaa Glu	ggc Gly 320	960
							agt Ser									1008
cgt Arg	att Ile	gcc Ala	gga Gly 340	cac His	cac His	tcg Ser	caa Gln	gaa Glu 345	att Ile	gat Asp	gca Ala	ata Ile	ctg Leu 350	gga Gly	tat Tyr	1056
gaa Glu	tac Tyr	ggc Gly 355	ccg Pro	gtt Val	gcc Ala	gtt Val	cac His 360	cgt Arg	gat Asp	gac Asp	atg Met	att Ile 365	acc Thr	cgt Arg	taa *	1104
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gcg Ala	caa Gln	ctc Leu	tcc Ser 20	agc Ser	cgc Arg	gaa Glu	aaa Lys	aat Asn 25	ege Arg	gtg Val	ctg Leu	gaa Glu	aaa Lys 30	atc Ile	gcc Ala	96
gat Asp	gaa Glu	ctg Leu 35	gaa Glu	gca Ala	Gln	Ser	gaa Glu 40	Ile	Ile	Leu	Asn	gct Ala 45	aac Asn	gcc Ala	cag Gln	144
gat Asp	gtt Val 50	gct Ala	gạc Asp	gcg Ala	cga Arg	gcc Ala 55	aat Asn	ggc Gly	ctt Leu	agc Ser	gaa Glu 60	gcg Ala	atg Met	ctt Leu	gac Asp	192
cgt Arg 65	ctg Leu	gca Ala	ctg Leu	acg Thr	ccc Pro 70	gca Ala	cgg Arg	ctg Leu	aaa Lys	ggc Gly 75	att Ile	gcc Ala	gac Asp	gat Asp	gta Val 80	240
cgt Arg	cag Gln	gtg Val	tgc Cys	aac Asn 85	ctc Leu	gcc Ala	gat Asp	ccg Pro	gtg Val 90	Gly	cag Gln	gta Val	atc Ile	gat Asp 95	ggc Gly	288
	~+·	cta	aac.	age	aac	ctg	cgt									336
				Ser		Leu	Arg	Leu 105	Glu	Arg	Arg	Arg	Val 110	Pro	Leu	

Gly	Val	Ile 115	Gly	Val	Ile	Tyr	Glu 120	Ala	Arg	Pro	Asn	Val 125	Thr	Val	Asp	
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	aaa Lys															480
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	aat Asn															576
	atc Ile															624
	cgt Arg 210															672
_	cat His			_	_	_	_	_			_	_	_			720
	atc Ile															768
	acg Thr															816
	agc Ser															864
	gca Ala 290															912
	gcc Ala															960
	atc Ile	_	-	_		_		_		_			_	_		1008
	aca Thr				_			_			_	_	_		_	1056
	cgt Arg															1104

355 360 365 tet acg egt ttt acc gac ggc egg cag ttt ggt etg ggt geg gaa gtg Ser Thr Arg Phe Thr Asp Gly Gly Gln Phe Gly Leu Gly Ala Glu Val 375 gcg gta agc aca caa aaa ctc cac gcg cgt ggc cca atg ggg ctg gaa 1200 Ala Val Ser Thr Gln Lys Leu His Ala Arg Gly Pro Met Gly Leu Glu gea etg acc act tac aag tgg atc ggc att ggt gat tac acc att cgt Ala Leu Thr Thr Tyr Lys Trp Ile Gly Ile Gly Asp Tyr Thr Ile Arg 405 gcg taa 1254 Ala * <210> 166 <211> 561 <212> DNA <213> Escherichia coli <220> <221> CDS <222> (1) ... (561) atg atg aca agg cag gca tca atg aaa ggc ttc cca att gcg cat att Met Met Thr Arg Gln Ala Ser Met Lys Gly Phe Pro Ile Ala His Ile 10 ttt cac cct tca atc ccg cca atg cac gca gtg gtt aac aat cac aat Phe His Pro Ser Ile Pro Pro Met His Ala Val Val Asn Asn His Asn aga aat att gat tat tgg acg gta aaa aga aag ttt gca gaa att gtc 144 Arg Asn Ile Asp Tyr Trp Thr Val Lys Arg Lys Phe Ala Glu Ile Val 40 tcc acc aat gac gtt aat aaa att tac agt ata agt aat gaa ctg cgg 192 Ser Thr Asn Asp Val Asn Lys Ile Tyr Ser Ile Ser Asn Glu Leu Arg aga gta tta tct gca ata act gca ttg aat ttc tat cat ggc gat gtt Arg Val Leu Ser Ala Ile Thr Ala Leu Asn Phe Tyr His Gly Asp Val 65 cct tct gtc atg atc cga atc caa ccg gaa aat atg agt cca ttc att 288 Pro Ser Val Met Ile Arg Ile Gln Pro Glu Asn Met Ser Pro Phe Ile 85 90 ata gat att tet aca gga gaa cat gat gat tat atc ata caa aca tta Ile Asp Ile Ser Thr Gly Glu His Asp Asp Tyr Ile Ile Gln Thr Leu

Asp Val Gly Thr Phe Ala Pro Phe Gly Glu Gln Cys Thr Cys Ser Ala 115 120 125

105

gat gta ggc act ttt gca cct ttt ggt gaa caa tgt act tgc tca gcc

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_			ttc Phe		_		_	_								480
			acc Thr													528
			cat His 180							tga *						561
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_	-		atg Met 20		_			_	_							96
			gca Ala													144
			tta Leu													192
			ttt Phe													240
tat Tyr	aat Asn	gtc Val	tcg Ser	tct Ser 85	ctt Leu	cgt Arg	ctg Leu	gat Asp	ttt Phe 90	tta Leu	ggt Gly	tat Tyr	aac Asn	gcc Ala 95	caa Gln	288
att Ile	att Ile	caa Gln	cga Arg 100	tcg Ser	gac Asp	aat Asn	act Thr	tgt Cys 105	gaa Glu	ctt Leu	acc Thr	att Ile	aat Asn 110	gaa Glu	ccg Pro	336
			cag Gln													384
			att Ile													432

130 135 140 tgt ggg act gga gat atc gtt gat cta tcc tct ctg gac tta cgt aat 480 Cys Gly Thr Gly Asp Ile Val Asp Leu Ser Ser Leu Asp Leu Arg Asn 155 145 gtc gat tta gat tat tat gat ttc aca gat aaa cat atg gct aat act 528 Val Asp Leu Asp Tyr Tyr Asp Phe Thr Asp Lys His Met Ala Asn Thr 170 165 att tta aat cct ttt aaa ttg aat tca aca aat ttt act aat gcc aac 576 Ile Leu Asn Pro Phe Lys Leu Asn Ser Thr Asn Phe Thr Asn Ala Asn 180 185 atg ttt cag gtt aat ttt gtt agt tca aca caa aac gcc aca atc tcc 624 Met Phe Gln Val Asn Phe Val Ser Ser Thr Gln Asn Ala Thr Ile Ser 195 200 tgg gat tat tta cta aaa ata acg cct gtt tta ata agc att agc gat 672 Trp Asp Tyr Leu Leu Lys Ile Thr Pro Val Leu Ile Ser Ile Ser Asp 210 atg tat tot gaa gaa aaa atc aag ttt gtc gaa agt tgt tta aat gag Met Tyr Ser Glu Glu Lys Ile Lys Phe Val Glu Ser Cys Leu Asn Glu 235 225 cct gga gac att acc gaa gaa caa tta aaa att atg aga ttt gca att 768 Pro Gly Asp Ile Thr Glu Glu Glu Leu Lys Ile Met Arg Phe Ala Ile 250 ata aaa tot ata oca agg goa act ott aca gat aaa tta gaa aat gaa 816 Ile Lys Ser Ile Pro Arg Ala Thr Leu Thr Asp Lys Leu Glu Asn Glu 260 265 tta aca aaa gaa ata tat aaa agc tca tcg aaa atc atc aat tgc ttg 864 Leu Thr Lys Glu Ile Tyr Lys Ser Ser Ser Lys Ile Ile Asn Cys Leu 280 275 aac aga att aaa tta aca gag atg aaa gaa ttc tca tca gaa aaa ata 912 Asn Arg Ile Lys Leu Thr Glu Met Lys Glu Phe Ser Ser Glu Lys Ile 290 **295** 300 tat gat tac atc gat ata atc att gaa gat tat gaa aat acc aaa gaa 960 Tyr Asp Tyr Ile Asp Ile Ile Ile Glu Asp Tyr Glu Asn Thr Lys Glu 305 310 aat get tat etg gte gte eec caa att aat tat act atg gat tta aac Asn Ala Tyr Leu Val Val Pro Gln Ile Asn Tyr Thr Met Asp Leu Asn 325 ata gaa gac tct agc tca gaa gag tta ctt tca gat aat acc ctc gag 1056 Ile Glu Asp Ser Ser Ser Glu Glu Leu Leu Ser Asp Asn Thr Leu Glu 340 350 aaa gac gaa aat tot cog gac aat ggc ttt gag gtc ggg gaa tat aac 1104 Lys Asp Glu Asn Ser Pro Asp Asn Gly Phe Glu Val Gly Glu Tyr Asn 355 aca tat gaa gca tat aac tca gag aag caa tat ttt acc aga gag gac Thr Tyr Glu Ala Tyr Asn Ser Glu Lys Gln Tyr Phe Thr Arg Glu Asp 370

	acg Thr															1188
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	0> 1> C 2> (:		. (94	8)												
gtg	0> 10 tgt Cys	cat														48
	ttt Phe															96
	att Ile															144
	agc Ser 50															192
	ttt Phe															240
	gcc Ala															288
	tgg Trp															336
	ctc Leu															384
	gta Val 130															432
tta Leu 145	caa Gln	cac His	gcg Ala	acc Thr	gaa Glu 150	gcc Ala	agt Ser	gaa Glu	tac Tyr	acg Thr 155	tta Leu	att Ile	ttg Leu	cta Leu	ctt Leu 160	480
	ctc Leu															528
att	gtc	ctt	aat	cgc	cgg	gga	atg	att	gtc	gcc	gtg	gtg	gtg	gtt	gtc	576

Ile	Val	Leu		Arg	Arg	Gly	Met		Val	Ala	Val	Val		Val	Val		
agt	tca	<b>+</b> +=	180	aat	ggt	tta	att	185 aac	acc	ttt	att	ctt	190	ctc	CCC	- 624	
Ser	Ser	Leu 195	Ile	Gly	Gly	Leu	Ile 200	Asn	Ala	Phe	Ile	Leu 205	Asp	Leu	Pro		
Ile	aat Asn 210	acc Thr	gcg Ala	ctg Leu	gca Ala	atg Met 215	gcc Ala	tcc Ser	ggt Gly	ttc Phe	ggc Gl <i>y</i> 220	tgg Trp	tat Tyr	tct Ser	ctt Leu	672	
					acc Thr 230											720	
gcg Ala	ttt Phe	ttt Phe	aat Asn	gat Asp 245	ctg Leu	gcc Ala	cgt Arg	gaa Glu	ctg Leu 250	att Ile	gct Ala	att Ile	atg Met	ttg Leu 255	atc Ile	768	
					cgc Arg											816	
					ttc Phe											864	
ctg Leu	gat Asp 290	atg Met	gtc Val	ccg Pro	gcg Ala	gca Ala 295	att Ile	gtt Val	cac His	ggt Gly	ttt Phe 300	att Ile	ctt Leu	agc Ser	ctg Leu	912	
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Met 1	Gln	Asn	Thr	Thr 5	His	Asp	Asn	Val	Ile	Leu	Glu	Leu	Thr	Val 15	Arg		
aac Asn	cat His	ccg Pro	ggc Gly 20	gta Val	atg Met	acc Thr	cac His	gtt Val 25	tgt Cys	ggc	ctt Leu	ttt Phe	gcc Ala 30	ege Arg	cgc Arg	96	
gct Ala	ttt Phe	aac Asn 35	gtt Val	gaa Glu	ggc Gly	att Ile	ctt Leu 40	tgt Cys	ctg Leu	ccg Pro	att Ile	cag Gln 45	gac Asp	agc Ser	gac Asp	144	
aaa Lys	age	cat	atc	tgg	cta	ctq	gtc	aat	gac	gac	cag	cgt	ctg	gag	cag	192	

	ata Ile															240
	cag Gln															288
taa *																291
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	ttt Phe															96
	att Ile															144
	acg Thr 50															192
	atc Ile															240
	gcc Ala															288
_	gcg Ala		_	_			_	_		_				_	_	336
	gcc Ala															384
	atc Ile 130															432
gaa	gaa	ctc	ccg	cag	gtc	atg	agc	gat	gcc	ttc	cgc	att	gcg	caa	tca	480

	31u 145	Glu	Leu	Pro	Gln	Val 150	Met	Ser	Asp	Ala	Phe 155	Arg	Ile	Ala	Gln	Ser 160	
9	ggc 31y	cgc Arg	cca Pro	ggc	ccg Pro 165	gtg Val	tgg Trp	ata Ile	gac Asp	att Ile 170	cct Pro	aag Lys	gat Asp	gtg Val	caa Gln 175	acg Thr	528
															gcc Ala		576
															atg Met		624
															atc Ile		672
1															cct Pro		720
															ccg Pro 255		768
															tat Tyr		816
															gat Asp		864
															atc Ile		912
															ccg Pro		960
															atc Ile 335		1008
															gcg Ala		1056
															ccg Pro		1104
															gac Asp		1152 ·
															gcg Ala		1200

385					390					395					400	
gct Ala	tat Tyr	ccg Pro	ctc Leu	aat Asn 405	cgċ Arg	cca Pro	cgc Arg	cag Gln	tgg Trp 410	ctg Leu	acc Thr	tcc Ser	ggt Gly	999 Gly 415	ctg Leu	1248
ggc Gly	acg Thr	atg Met	ggt Gly 420	ttt Phe	ggc Gly	ctg Leu	cct Pro	gcg Ala 425	gcg Ala	att Ile	ggc Gly	gct Ala	gcg Ala 430	ctg Leu	gcg Ala	1296
						ttg Leu										1344
_			_		_	gcg Ala 455		_	_	_		_	_	_	_	1392
						aac Asn										1440
_	_	_				caa Gln		-		_	_			_		1488
						att Ile										1536
						gat Asp										1584
	_			-		ctg Leu 535				_		_	_	_	_	1632
	_		_	_		ccg Pro							_	_		1680
	gaa Glu															1689
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	.> CI		(99)													
atg		act				aac Asn										48

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165 170 175 cat cag acc aag aaa ggc aat cag tgg cac ttt ggc atg aag gcc cac 576 His Gln Thr Lys Lys Gly Asn Gln Trp His Phe Gly Met Lys Ala His 185 att ggt gtc gat gcc aag agt ggc ctg acc cac agc ctg gtc acc acc 624 Ile Gly Val Asp Ala Lys Ser Gly Leu Thr His Ser Leu Val Thr Thr 200 geg gee aac gag cat gac etc aat eag etg ggt aat etg etg eat gga 672 Ala Ala Asn Glu His Asp Leu Asn Gln Leu Gly Asn Leu Leu His Gly 210 215 gag gag caa ttt gtc tca gcc gat gcc ggc tac caa ggg gcg cca cag 720 Glu Glu Gln Phe Val Ser Ala Asp Ala Gly Tyr Gln Gly Ala Pro Gln 225 230 cgc gag gag ctg gcc gag gtg gat gtg gac tgg ctg atc gcc gag cgc 768 Arg Glu Glu Leu Ala Glu Val Asp Val Asp Trp Leu Ile Ala Glu Arg 245 250 ccc ggc aag gta aga acc ttg aaa cag cat cca cgc aag aac aaa acg 816 Pro Gly Lys Val Arg Thr Leu Lys Gln His Pro Arg Lys Asn Lys Thr 260 265 gcc atc aac atc gaa tac atg aaa gcc agc atc cgg gcc agg gtg gag 864 Ala Ile Asn Ile Glu Tyr Met Lys Ala Ser Ile Arg Ala Arg Val Glu 275 280 cac cca ttt cgc atc atc aag cga cag ttc ggc ttc gtg aaa gcc aga 912 His Pro Phe Arg Ile Ile Lys Arg Gln Phe Gly Phe Val Lys Ala Arg 290 295 300 tac aag ggg ttg ctg aaa aac gat aac caa ctg gcg atg tta ttc acg 960 Tyr Lys Gly Leu Leu Lys Asn Asp Asn Gln Leu Ala Met Leu Phe Thr 305 310 315 ctg gcc aac ctg ttt cgg gcg gac caa atg ata cgt cag tgg gag aga 1008 Leu Ala Asn Leu Phe Arg Ala Asp Gln Met Ile Arg Gln Trp Glu Arg tct cac taa 1017 Ser His * <210> 173 <211> 474 <212> DNA <213> Escherichia coli <220> <221> CDS <222> (1) ... (474) <400> 173 atg gta tat ata ata atc gtt tcc cac gga cat gaa gac tac atc aaa Met Val Tyr Ile Ile Ile Val Ser His Gly His Glu Asp Tyr Ile Lys 10

	tta Leu															96
	cgc Arg															144
	gca Ala 50															192
	aat Asn /															240
gat Asp	gat Asp	gat Asp	tac Tyr	att Ile 85	ttg Leu	ttt Phe	ttg Leu	aat Asn	ccc Pro 90	gat Asp	atc Ile	atc Ile	atg Met	aag Lys 95	cat His	288
	gat Asp															336
	agt Ser															384
	tcc Ser 130															432
atg Met 145	tta Leu	Gly ggg	att Ile	aag Lys	gaa Glu 150	ggt Gly	gcg Ala	aac Asn	aag Lys	tcc Ser 155	ctg Leu	ata Ile	tga *			474
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	0> 1> CI 2> (:		. (11:	19)												
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	cca Pro				_				_	_	-					96
	aat Asn															144
gaa	agt	tat	cca	tgg	gtt	aaa	ttc	att	gag	ttt	cct	gag	gtt	aaa	ggg	192

Glu	Ser 50	Tyr	Pro	Trp	Val	Lys 55	Phe	Ile	Glu	Phe	Pro 60	Glu	Val	Lys	Gly	
_				cgt Arg	_			_		_	_	_				240
				aat Asn 85												288
_		_	-	act Thr			-				_				_	336
				gga Gly				-	_			_			_	384
				aaa Lys	_				_							432
				gca Ala			_					_		_		480
		-		tat Tyr 165							_	_			~	528
				gat Asp		-				_	_	_				576
_				tct Ser	_	_						_	_		_	624
_				tac Tyr					_	_	-			_		672
				att Ile												720
				tat Tyr 245												768
				tac Tyr												816
		_		gtt Val	_						_				_	864
				gct Ala												912

290 295 300 ttc cca ttt act aga gaa act ctt ggt agt tat gaa aag aaa gct ttt Phe Pro Phe Thr Arg Glu Thr Leu Gly Ser Tyr Glu Lys Lys Ala Phe ttt gat tct aat aac gat gac atg tta gtt aaa ctt att att gac ttc 1008 Phe Asp Ser Asn Asn Asp Asp Met Leu Val Lys Leu Ile Ile Asp Phe aaa aaa ggt aac ctc aaa aaa gat atc tct gat gca aat ttc att tat 1056 Lys Lys Gly Asn Leu Lys Lys Asp Ile Ser Asp Ala Asn Phe Ile Tyr Arg Asn Glu Asn Val Leu Val Gly Phe Asp Glu Leu Val Asn Phe Ile 1119 act gaa gaa cat tga Thr Glu Glu His * 370 <210> 175 <211> 591 <212> DNA <213> Escherichia coli <220> <221> CDS <222> (1) ... (591) atg atc tta aaa ctc gct aaa cga tat ggt ctc tgt ggt ttt att cgg Met Ile Leu Lys Leu Ala Lys Arg Tyr Gly Leu Cys Gly Phe Ile Arg ctt gtt aga gat gtc tta ttg act cgt gta ttt tac cgg aac tgt aga Leu Val Arg Asp Val Leu Leu Thr Arg Val Phe Tyr Arg Asn Cys Arg att att ega ttt eec tge tat att ege aat gat ggt age att aat ttt Ile Ile Arg Phe Pro Cys Tyr Ile Arg Asn Asp Gly Ser Ile Asn Phe ggt gaa aat ttc aca agt gga gtc ggt ctc agg ctg gat gca ttt gga 192 Gly Glu Asn Phe Thr Ser Gly Val Gly Leu Arg Leu Asp Ala Phe Gly 55 cgt ggc gtg att ttt ttt tcc gat aat gtg caa gtt aac gac tat gtt 240 Arg Gly Val Ile Phe Phe Ser Asp Asn Val Gln Val Asn Asp Tyr Val 70 cat atc gcc tca att gag agc gtt acg ata ggt cgg gat acg ctt att 288 His Ile Ala Ser Ile Glu Ser Val Thr Ile Gly Arg Asp Thr Leu Ile 85 90 gca agt aaa gta ttt att acc gat cat aat cac ggt tcc ttt aag cac Ala Ser Lys Val Phe Ile Thr Asp His Asn His Gly Ser Phe Lys His 100 105

ser Asp Pro Met Ser Ser Pro Asn Ile Pro Pro Asp Met Arg Thr Leu 115 120 125	384
gaa tot toa got gtt gta att ggo cag agg gtt tgg ttg ggt gag aat Glu Ser Ser Ala Val Val Ile Gly Gln Arg Val Trp Leu Gly Glu Asn 130 135 140	432
gtg acg gtt ttg cct gga aca att att ggt aat gga gtc gta gtc ggc Val Thr Val Leu Pro Gly Thr Ile Ile Gly Asn Gly Val Val Val Gly 145 150 155 160	480
gcc aat tct gtt gtt aga ggt tct att ccc gaa aat act gtc att gcg Ala Asn Ser Val Val Arg Gly Ser Ile Pro Glu Asn Thr Val Ile Ala 165 170 175	528
gga gta cca gca aaa atc ata aag aaa tac aat cat gag acc aaa tta Gly Val Pro Ala Lys Ile Ile Lys Lys Tyr Asn His Glu Thr Lys Leu 180 185 190	576
tgg gaa aaa gca tag Trp Glu Lys Ala * 195	591
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<pre>&lt;221&gt; CDS &lt;222&gt; (1) (993)  &lt;400&gt; 176 atg tat ttt ttg aat gat tta aat ttc tct aga cgc gat gct gga ttt Met Tyr Phe Leu Asn Asp Leu Asn Phe Ser Arg Arg Asp Ala Gly Phe 1</pre>	96
<pre>&lt;221&gt; CDS &lt;222&gt; (1) (993)  &lt;400&gt; 176 atg tat ttt ttg aat gat tta aat ttc tct aga cgc gat gct gga ttt Met Tyr Phe Leu Asn Asp Leu Asn Phe Ser Arg Arg Asp Ala Gly Phe 1</pre>	96 144
<pre>&lt;221&gt; CDS &lt;222&gt; (1) (993)  &lt;400&gt; 176 atg tat ttt ttg aat gat tta aat ttc tct aga cgc gat gct gga ttt Met Tyr Phe Leu Asn Asp Leu Asn Phe Ser Arg Arg Asp Ala Gly Phe 1</pre>	96 144 192

100 105 110 384 get acc tgt gat atg gtc ata agt cac aat cca caa atg aca aag tac Ala Thr Cys Asp Met Val Ile Ser His Asn Pro Gln Met Thr Lys Tyr 120 115 ctt agt aaa tat atg tct cag gat aaa atc aaa gac ata aaa ata ttt 432 Leu Ser Lys Tyr Met Ser Gln Asp Lys Ile Lys Asp Ile Lys Ile Phe 130 135 gat tac ctc gtc tca tct gat gtg gag cat cga gat gtt acg gat aag 480 Asp Tyr Leu Val Ser Ser Asp Val Glu His Arg Asp Val Thr Asp Lys 150 145 caa cga ggg gtc ata tat gct ggc aac ctt tct agg cat aaa tgt tct 528 Gln Arg Gly Val Ile Tyr Ala Gly Asn Leu Ser Arg His Lys Cys Ser 165 170 ttc ata tat act gaa gga tgc gat ttt act ctc ttt ggt gtc aac tat 576 Phe Ile Tyr Thr Glu Gly Cys Asp Phe Thr Leu Phe Gly Val Asn Tyr gaa aat aaa gat aat cct aaa tat ctt gga agt ttt gat gct caa tct Glu Asn Lys Asp Asn Pro Lys Tyr Leu Gly Ser Phe Asp Ala Gln Ser 200 ccg gaa aag att aac ctc cca ggc atg caa ttt gga ctc att tgg gat 672 Pro Glu Lys Ile Asn Leu Pro Gly Met Gln Phe Gly Leu Ile Trp Asp 210 215 220 gga gat tet gte gaa ace tgt agt ggt gee ttt gge gae tat tta aag 720 Gly Asp Ser Val Glu Thr Cys Ser Gly Ala Phe Gly Asp Tyr Leu Lys 225 230 235 ttt aat aac cct cat aag aca tct ctt tat ctt tca atg gaa ctt cca 768 Phe Asn Asn Pro His Lys Thr Ser Leu Tyr Leu Ser Met Glu Leu Pro 250 245 gta ttt ata tgg gat aaa gcc gcc ctt gcg gat ttc att gta gat aat 816 Val Phe Ile Trp Asp Lys Ala Ala Leu Ala Asp Phe Ile Val Asp Asn 260 265 aga ata gga tat gca gtg gga tca atc aaa gaa atg caa gag att gtt Arg Ile Gly Tyr Ala Val Gly Ser Ile Lys Glu Met Gln Glu Ile Val 275 gac tcc atg aca ata gaa act tat aag caa att agt gag aat aca aaa 912 Asp Ser Met Thr Ile Glu Thr Tyr Lys Gln Ile Ser Glu Asn Thr Lys 290 att att tet cag aaa att ega aca gga agt tae tte agg gat gtt ett 960 Ile Ile Ser Gln Lys Ile Arg Thr Gly Ser Tyr Phe Arg Asp Val Leu 305 315 gaa gag gtg atc gat gat ctt aaa act cgc taa 993 Glu Glu Val Ile Asp Asp Leu Lys Thr Arg

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325

330

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gct tt Ala Ph 305															960
atg gt Met Va				_				_			_	_		_	1008
aat ta Asn Ty															1056
tct tt Ser Ph					_	_		_				_	_		1104
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				cac His											336
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				ctt Leu											624
			_	ttt Phe	_		_		_			_		_	672
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gtt ggc gac g Val Gly Asp 6 305	du Pro T			Asn A					960
ctt ttt aag a Leu Phe Lys I			_			_			1008
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<pre>&lt;211&gt; 693 &lt;212&gt; DNA &lt;213&gt; Escheri &lt;220&gt; &lt;221&gt; CDS &lt;222&gt; (1) &lt;400&gt; 179 ttg aca tca t Met Thr Ser S 1 gag gtt ctt a Glu Val Leu A aat agt tgc t Asn Ser Cys S</pre>	(693)  cca ata a  Ser Ile T  5  acc atg g  Asn Met G  20  cca atg c  Ser Met H	acc aat Thr Asn Trigg ctt Gly Leu Tat tgc Tis Cys Tac tcg	tgt agt Cys Ser 2! caa ata Gln Ile 40	e Met G: 10 cgt ta Arg Ti atg ca Met P:	at aaa yr Lys ca gaa ro Glu tg tgg	agt constant age to the second	hr Asp 15  tt aca eu Thr 30  ca ccg er Pro	tgc Cys cgt Arg	96
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Asn Ala Arg Le	u Ser Gly 85	Tyr Ile	Phe V	/al Asp 90	Phe Ser	. Val	Ser 95	Phe	
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aat tac tgg cg Asn Tyr Trp Ai 130									432
gat gat ggt ct Asp Asp Gly Le 145									480
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ttc acc ata at Phe Thr Ile Me	t Gly Tyr								576
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				ccg Pro												432
_		-		cgt Arg	_					_				_	_	480
				cat His 165												528
_	_	_		agc Ser	_	_		_	_	_	_		_	_		576
				cgc Arg												624
Gln	_		-	ccg Pro		${\tt Gln}$	Thr		Arg	Leu		Ser	_			672
				ggt Gly												720
				gaa Glu 245												768
	_			gtg Val		-	-		_	_			_			816
_	_			ctg Leu	_					_		_	_	_	_	864

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cag cag agt gcc gcc att ttg ttc tgc gtc gaa ggc gat gca acg ttg Gln Gln Ser Ala Ala Ile Leu Phe Cys Val Glu Gly Asp Ala Thr Leu 340 345 350	
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				tct Ser												336
				gcc Ala												384
				cca Pro												432
				aac Asn												480
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_		Thr		ccg Pro	_	Trp	${\tt Gln}$	Ser	Ile		_	Thr		Gly		576
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				ttc Phe 245												768
gtg	cag	tac	atc	agc	atg	ggg	caa	att	ctt	tcc	atc	ccg	atg	att	gtc	816

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											ccg Pro						576
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7											gcg Ala 235						720
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_		atg Met	_		_		_				_				_	96

	cg ato er Met	Ala											144
Leu M	tg tco let Sei 50												192
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Leu S	ct gcg er Ala 30												432
	cg cag la Glr												480
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_	ag tgg ys Tr <u>r</u> 199	Lys	_		Ser	 Ile	_	_	Lys	 _			624
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-	cg ccg la Pro	_	_						_		_	_	720
	itg atg Met Met												768
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Gly Ala Thr Phe Pro Ala Pro Val Tyr Ala Lys Trp Ala Asp Thr Tyr

40

35

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				att Ile											336
				gaa Glu											384
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				aaa Lys											480
				999 Gly 165											528
		_		tgg Trp				-							576
				ctg Leu											624
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				ctg Leu											720
_	_	_	_	acc Thr 245	_	_			_		_	_		_	768
				acc Thr											816
_				att Ile				_			_			_	864

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				acc Thr								96
				aaa Lys								144
				aag Lys								192
				gcg Ala								240
				gaa Glu 85								288
				atc Ile								336
				aaa Lys								384
				Cys tgc								432

140 130 135 atg atc aac aac tgc acc acc ctc tcc cca gat tca gga gat atc gcc · 480 Met Ile Asn Asn Cys Thr Thr Leu Ser Pro Asp Ser Gly Asp Ile Ala 145 150 aat acg ttg aaa tca cgc cat gcg atg caa gag cgc act ttg cag cag Asn Thr Leu Lys Ser Arg His Ala Met Gln Glu Arg Thr Leu Gln Gln 170 165 ttt tta tgt caa cga caa gcg cgc ggg gaa atc ccg ccc cac tgt gac 576 Phe Leu Cys Gln Arg Gln Ala Arg Gly Glu Ile Pro Pro His Cys Asp 185 180 gtg aca cat ctg gca gaa ttc ctt aat tgt att att cag ggg atg tcg 624 Val Thr His Leu Ala Glu Phe Leu Asn Cys Ile Ile Gln Gly Met Ser 200 195 atc agc gca cgc gaa ggt gca tcg ctg gaa aaa ctg atg cag att gcc 672 Ile Ser Ala Arg Glu Gly Ala Ser Leu Glu Lys Leu Met Gln Ile Ala gga acg act ttg cgt tta tgg ccc gaa ctg gtg aaa taa 711 Gly Thr Thr Leu Arg Leu Trp Pro Glu Leu Val Lys * <210> 189 <211> 546 <212> DNA <213> Escherichia coli <220> <221> CDS <222> (1) ... (546) <400> 189 gtg cag gcc aaa att gcg gca tca aat acg ggt gaa ctg gat gcc ctg Met Gln Ala Lys Ile Ala Ala Ser Asn Thr Gly Glu Leu Asp Ala Leu 5 caa cag ctg gga ttc tcc ctg gta gaa ggt gaa gtt gat ttg gcg cta Gln Gln Leu Gly Phe Ser Leu Val Glu Gly Glu Val Asp Leu Ala Leu 20 ccc gtg aac aat gcc agt gat agc ggt gct gta gtg gca caa gag acc 144 Pro Val Asn Asn Ala Ser Asp Ser Gly Ala Val Val Ala Gln Glu Thr 35 gat att ccc gca tta cgt cag tta gcc agc gcc gca ttt gcg caa agc 192 Asp Ile Pro Ala Leu Arg Gln Leu Ala Ser Ala Ala Phe Ala Gln Ser egt ttt egt geg eeg tgg tat geg eet gae gee agt ege ttt tat 240 Arg Phe Arg Ala Pro Trp Tyr Ala Pro Asp Ala Ser Ser Arg Phe Tyr gca cag tgg att gaa aat gcc gtg cgc ggc acc ttt gat cat caa tgt Ala Gln Trp Ile Glu Asn Ala Val Arg Gly Thr Phe Asp His Gln Cys

ctg att tta c Leu Ile Leu A 1					_		_			_			336
cgg gaa ctc a Arg Glu Leu A 115			qaA										384
ggt gca ggt g Gly Ala Gly A 130		Leu											432
cgc ggt aaa a Arg Gly Lys T 145		_						_				_	480
gcg ctt aaa c Ala Leu Lys A													528
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gaa gcg gcg atc acc gac aaa acg cgc gtt atc gtg ccg gtc cat tac 384
Glu Ala Ala Ile Thr Asp Lys Thr Arg Val Ile Val Pro Val His Tyr
115 120 125

gcg ggt gtg gcc tgc gaa atg gac acc att atg gcg ttg gcg aaa aag 432
Ala Gly Val Ala Cys Glu Met Asp Thr Ile Met Ala Leu Ala Lys Lys
130 135 140

cat aat ttg ttt gtg gta gaa gat gcc gct cag ggc gtg atg tcc act
His Asn Leu Phe Val Val Glu Asp Ala Ala Gln Gly Val Met Ser Thr
145 150 155 160

tac aaa ggg cgt gca ctg gga acc att ggt cat att ggc tgc ttt agc 528
Tyr Lys Gly Arg Ala Leu Gly Thr Ile Gly His Ile Gly Cys Phe Ser
165 170 175

ttc cat gaa acc aaa aac tac acg gcg ggc ggt gaa ggc gcg gcg acg 576
Phe His Glu Thr Lys Asn Tyr Thr Ala Gly Gly Glu Gly Gly Ala Thr
180 185 190

ctg att aac gat aaa gcg tta atc gaa cga gcc gag atc atc cgt gaa 624 Leu Ile Asn Asp Lys Ala Leu Ile Glu Arg Ala Glu Ile Ile Arg Glu 195 200 205

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Thr Trp Arg Asp Ile Gly Ser Ser Tyr Leu Met Ser Asp Leu Gln Ala
225 230 235 240

gca tac ctg tgg gcg caa ctg gaa gca gcg gat cgt atc aac cag caa 768
Ala Tyr Leu Trp Ala Gln Leu Glu Ala Ala Asp Arg Ile Asn Gln Gln
245 250 255

cgt ctg gcg ctg tgg caa aac tac tac gat gcg tta gcg cct ctg gcg
Arg Leu Ala Leu Trp Gln Asn Tyr Tyr Asp Ala Leu Ala Pro Leu Ala
260 265 270

aaa gcc ggg cgt atc gag ctg ccg tcg att ccc gat ggc tgc gtg cag
Lys Ala Gly Arg Ile Glu Leu Pro Ser Ile Pro Asp Gly Cys Val Gln
275
280
285

aac gcg cat atg ttc tac att aaa ctg cgg gat att gat gac cgg agc
Asn Ala His Met Phe Tyr Ile Lys Leu Arg Asp Ile Asp Asp Arg Ser
290
295
300

gcg ttg att aac ttt ctg aaa gaa gcg gaa atc atg gcg gtg ttt cat
Ala Leu Ile Asn Phe Leu Lys Glu Ala Glu Ile Met Ala Val Phe His
305 310 315 320

tac att ccg ctg cac ggt tgc cct gcg ggg gaa cac ttt ggt gag ttc

Tyr Ile Pro Leu His Gly Cys Pro Ala Gly Glu His Phe Gly Glu Phe

325

330

335

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His Gly Glu Asp Arg Tyr Thr Thr Lys Glu Ser Glu Arg Leu Leu Arg
340 345 350

ctg ccg ctg ttc tac aac ctg tcg ccc gtc aat cag cgt acg gta att Leu Pro Leu Phe Tyr Asn Leu Ser Pro Val Asn Gln Arg Thr Val Ile 355 360 365	1104
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gtg ctc ggc gtg ctt gcc ggg gct ggc atc ttt aac ggt gta acc aaa Val Leu Gly Val Leu Ala Gly Ala Gly Ile Phe Asn Gly Val Thr Lys 50 55 60	192
tac gtt gcc cag tac cat gat aat ccg caa cag ctg cgc cgc gtg gtc Tyr Val Ala Gln Tyr His Asp Asn Pro Gln Gln Leu Arg Arg Val Val 65 70 75 80	240
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gtt ttt gtg ctg gca gct gcg cca atc agc cag gga ttg ttt ggt aat Val Phe Val Leu Ala Ala Ala Pro Ile Ser Gln Gly Leu Phe Gly Asn 100 105 110	336
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atc gcc tgg ggc aac ctg tta ctg gcg ctg atg aaa ggc ttt cgc gat Ile Ala Trp Gly Asn Leu Leu Leu Ala Leu Met Lys Gly Phe Arg Asp 130 135 140	432
gcc gca ggt aat gcg tta tcg ctg att gtc ggc agc ttg att ggc gtt Ala Ala Gly Asn Ala Leu Ser Leu Ile Val Gly Ser Leu Ile Gly Val 145 150 155 160	480
ctc gcg tac tac gtc agt tac cgt ttg ggc ggt tat gaa ggg gcg ttg	528

Leu	Ala	Tyr	Тут	Val 165	Ser	Tyr	Arg	Leu	Gly 170	Gly	Tyr	Glu	Gly	Ala 175	Leu	
					att Ile											576
_	_			_	ggt Gly	_		_		_		_			_	624
					gca Ala											672
		_	_		acc Thr 230	_		-	_			_	_	_		720
					tat Tyr											768
					gat Asp											816
_	-		_	_	ccc Pro	_	_	_			_	_	_	_	_	864
					gtt Val											912
					acc Thr 310											960
_	_	_	_		aaa Lys			_	_	_	_			-		1008
					gtg Val											1056
					gcg Ala											1104
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					gcg Ala 390											1200
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1251

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cag gac Gln Asp	agc aaa Ser Lys 180	gcg (	tgg Trp	ctg Leu	ttt Phe	ttc Phe 185	ctc Leu	gtc Val	agc Ser	acg Thr	gtc Val 190	gcc Ala	ttt Phe	576
ggc ttg Gly Leu														624
atc gca Ile Ala 210			Phe											672
tcg ttg Ser Leu 225		Leu Z												720
ttc tgg Phe Trp														768
gcg ttc Ala Phe														816
	Leu Ala 275	Leu 1	Leu	Leu	Gln 280	Asn	Tyr	Asp	Asn	Ile 285	Asp	Phe	Gln	864
ggc ctg Gly Leu 290	gct cca Ala Pro	att g	Val	cgc Arg 295	gat Asp	ttc Phe	tat Tyr	gtc Val	ttt Phe 300	atc Ile	cct Pro	tcc Ser	tgg Trp	912
ctg tgg Leu Trp 305		Arg :												960
acc tgg Thr Trp														1008
ctt ata Leu Ile														1056
ggg gcg Gly Ala														1104
gag ctg Glu Leu 370			Glu											1152
agt ttc Ser Phe 385		Gly a					Met							1200
ggg ctg Gly Leu														1248
ggc gca	tgt ctg	atg	atc	gca	aaa	ctg	ttg	tac	tgg	ctt	ttt	gaa	agc	1296

Gly Ala Cys Leu Met Ile Ala Lys Leu Leu Tyr Trp Leu Phe Glu Ser 425 gcc gga ctc att cat aaa cgt aca aaa tca tcg ctc cgg acg cag gtt 1344 Ala Gly Leu Ile His Lys Arg Thr Lys Ser Ser Leu Arg Thr Gln Val 440 gaa gga taa 1353 Glu Gly * 450 <210> 193 <211> 741 <212> DNA <213> Escherichia coli <220> <221> CDS <222> (1) ... (741) <400> 193 atg aat aac acc acg gca cca acc tat acg ctg cgt ggc tta cag 48 Met Asn Asn Asn Thr Thr Ala Pro Thr Tyr Thr Leu Arg Gly Leu Gln ttg att ggt tgg cgt gat atg cag cac gcc ctc gat tat ctg ttt gct 96 Leu Ile Gly Trp Arg Asp Met Gln His Ala Leu Asp Tyr Leu Phe Ala 20 gac ggg cag ctt aag cag gga acg ctg gtt gcc att aat gct gaa aaa 144 Asp Gly Gln Leu Lys Gln Gly Thr Leu Val Ala Ile Asn Ala Glu Lys 40 atg ctg act att gaa gat aac gcc gag gtc agg gag tta att aac gct 192 Met Leu Thr Ile Glu Asp Asn Ala Glu Val Arg Glu Leu Ile Asn Ala 55 gcc gaa ttt aaa tat gcg gat ggc atc agc gtt gta cgt tca gta cgt 240 Ala Glu Phe Lys Tyr Ala Asp Gly Ile Ser Val Val Arg Ser Val Arg aaa aag tac ceg cag geg cag gtt tec ege gtt gee ggt gee gat ete Lys Lys Tyr Pro Gln Ala Gln Val Ser Arg Val Ala Gly Ala Asp Leu 85 tgg gaa gag ctg atg gcg cgc gca ggc aaa gaa ggg acg ccg gta ttt 336 Trp Glu Glu Leu Met Ala Arg Ala Gly Lys Glu Gly Thr Pro Val Phe 100 ctt gtg ggc ggt aaa cct gaa gtg ctg gcg caa act gaa gct aaa ctg 384 Leu Val Gly Gly Lys Pro Glu Val Leu Ala Gln Thr Glu Ala Lys Leu 115 120 ege aac cag tgg aat gtg aat atc gtt ggc agt cag gat ggt tat ttt 432 Arg Asn Gln Trp Asn Val Asn Ile Val Gly Ser Gln Asp Gly Tyr Phe 130 135 aaa ccc gag cag cgt cag gcg ctg ttt gaa cgc att cat gcc agc ggt 480 Lys Pro Glu Gln Arg Gln Ala Leu Phe Glu Arg Ile His Ala Ser Gly 145 155

					gtt Val											528
-	_	_	_	_	ctg Leu	-			_		_		_		_	576
	Gly			_	gtt Val					_		_	_	_		624
			_	_	GIY 999	_					_	_		_	_	672
_	_	_		_	cgt Arg 230	_		_	-	_	_			_		720
			GJA GGC		cta Leu	tga *										741
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		_	-		ttt Phe						_		_	_		96
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_	-	_			tct Ser							_			_	192
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			acg Thr										144
			ctc Leu							Ala			192
			ttg Leu										240
			caa Gln										288
			gat Asp 100										336
			ccg Pro										384
Met	Gly	Gly	ggt Gly	Phe	Tyr	Asp	Arg	Thr	Leu	Gln	Trp		432
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				atg Met 85												288
				tcg Ser												336
				gaa Glu												384
gat Asp	atc Ile 130	cgc Arg	gtc Val	atc Ile	ctc Leu	atc Ile 135	aaa Lys	ctt Leu	gcc Ala	gac [.] Asp	cgt Arg 140	acc Thr	cac His	aac Asn	atg Met	432
				tca Ser												480
				att Ile 165												528
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				atc Ile												672
				ata Ile												720
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				tac Tyr												816
				ctg Leu												864
				gac Asp												912
				tcg Ser												960
cag	atc	cgt	acc	gaa	gat	atg	gac	cag	atg	gcg	gag	atg	ggt	gtt	gcc	1008

Gln	Ile	Arg	Thr	GLu 325	Asp	Met	Asp	Gln	Met 330	Ala	Glu	Met	Gly	VaI 335	Ala	
gcg ( Ala )																1056
atc (																1104
gcc (		_			_				_	_			_			1152
Pro 2																1200
ect o				_			_		_		-				_	1248
atc q			_	_			_	_	_	_	_	_			_	1296
ctg (																1344
ccg g Pro (																1392
aaa g Lys 2 465																1440
gat i																1488
agc o																1536
gat ( Asp 1																1584
ctt g Leu (																1632
gac g Asp. 2 545	gcc Ala	tcc Ser	att Ile	cca Pro	ccg Pro 550	gca Ala	acc Thr	caa Gln	agc Ser	cac His 555	gga Gly	cat His	ctg Leu	ccc Pro	att Ile 560	1680
aaa g Lys (	ggt Gly	gcc Ala	gat Asp	Gly ggc	gtg Val	ctg Leu	atc Ile	acc Thr	ttt Phe	gcg Ala	aaa Lys	tgc Cys	tgc Cys	cgc Arg	cct Pro	1728

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60

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55

gcg Ala 65																240
gat Asp				cat His 85												288
cat His			_	aac Asn	_	_	_		_	_		_			_	336
_		_		ttg Leu	_		_	_		_			_	_	_	384
gca Ala				gcg Ala												432
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atg Met				gca Ala												576
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						_		_	_		-		gcc Ala	_		192
													cgg Arg			240
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			_		_	_			_	_	-	_	ggc Gly 110			336
													gcg Ala			384
													cca Pro			432
													gta Val			480
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													gga Gly 190			576
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_		_	_	-	_			_		_			cgt Arg	_	-	672
													gcc Ala			<b>720</b>
													aat Asn			768
_						_	_		-		-		acg Thr		_	816

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510

505

500

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acg ggt aat gct gaa ttt aaa gtg gcg gat tta ctg cgc gat cag gcg Thr Gly Asn Ala Glu Phe Lys Val Ala Asp Leu Leu Arg Asp Gln Ala 645 650 655	1968
atg atc ccg gaa gtt cag cgc ctg gca cgc cat att cac gaa cgt tac Met Ile Pro Glu Val Gln Arg Leu Ala Arg His Ile His Glu Arg Tyr 660 665 670	2016
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						gac Asp										144
	_		_			tgt Cys 55		_	_	_					_	192
						ggt Gly										240
	_		_	_		atc Ile		_							_	288
	_		_			gcc Ala		_			_	_	_	_		336
_				_	_	gtt Val		_	_	_			_	_		384
att	gtc	acc	++-										مقمقيت			430
	_	_			_	Asp 135	-		_	_	_	_			_	432
Ile ttt	Val 130 gcc	Ala	Phe ggt	Ile aac	Met	Asp	Val	Ile gtg	Pro	Ala	Ser 140 ttt	Val	Ile gta	Gly	Ala	480
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ttt Phe 145 ggt Gly gtc Val	Val 130 gcc Ala ttt Phe atc Ile	Ala agc Ser gcg Ala gaa Glu	ggt Gly ctc Leu agt ser 180	aac Asn cac His 165 ttc Phe	Met  att Ile 150 cgt Arg tcg ser att	Asp 135 ctg Leu ctg Leu	val cag Gln ggc Gly gtc val	gtg Val agc ser atc Ile 185	ctg Leu aaa Lys 170 ttc Phe	Ala ctg Leu 155 ggc Gly ggc Gly	ser 140 ttt Phe caa Gln atc Ile	yal gcc Ala ctg Leu atc Ile	gta Val att Ile aat Asn 190	Gly ctg Leu ttt Phe 175 atg Met	Ala  ttt Phe 160 aac Asn  atc Ile	480 528
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					gcg Ala											144
					tat Tyr											192
					gac Asp 70											240
					gcc Ala											288
					att Ile											336
					gtc Val											384
					cgg Arg											432
					gca Ala 150											480
					atc Ile											528
_	_	Ăla	_	Ile	ttc Phe		Leu		Lys	_				-		576
cgt Arg	cgt Arg	cag Gln 195	cca Pro	ttt Phe	cac His	att Ile	cgt Arg 200	acc Thr	act Thr	att Ile	ggt Gly	aac Asn 205	ttt Phe	gcg Ala	gcg Ala	624
					egt Arg											672
					ttc Phe 230											720
					gtc Val											768
cta	aac	att	gtt	ttt	ctg	ttc	gtg	atg	acc	atc	ttt	aac	agc	cgc	ttc	816

Leu	Asn	Ile	Val 260	Phe	Leu	Phe	Val	Met 265	Thr	Ile	Phe	Asn	Ser 270	Arg	Phe	
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	ttt Phe 290															912
	ttt Phe															960
	atg Met															1008
	atg Met			_	_		-	_	_				_			1056
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	tgg Trp 370															1152
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	gcc Ala															96
	gtc Val	_		_				_			_		_	_	_	144
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	aag Lys 130															432
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	•			gaa Glu	_		_			_	_					192
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				gcg Ala 85	_		_	_	_	_		_				288
	_		_	gac Asp		-	_	_	Gln				_			336
_	_	_	_	att Ile	_					_		_				384
_	_			acc Thr	_	_			_		_		_			432
			-	aat Asn			_	-	_					_	-	480
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	-			gat Asp					_	_		_				576
				aaa Lys	_		_		_		_		_	_		624
-			-	ctg Leu	_	_		_	-							672
				aaa Lys												720
				ata Ile 245												768
_	_	_		aag Lys		_	_		_	_			_		_	816

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10

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	aaa Lys															240
cag Gln	gga Gly	cgt Arg	tat Tyr	gaa Glu 85	ggc	ttt Phe	ggt	cct Pro	aat Asn 90	Gly	tca Ser	atg Met	att Ile	atc Ile 95	gcc Ala	288
	aca Thr															336
att Ile	ttc Phe	aat Asn 115	aaa Lys	aaa Lys	ggc Gly	ggc Gly	aat Asn 120	atc Ile	gga Gly	gcg Ala	gca Ala	ggt Gly 125	tct Ser	gtc Val	agc Ser	384
	atg Met 130															432
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Lys Ala Ala Thr Glu Pro Ala His Arg Pro Ala Phe Phe Arg Thr Leu
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Val Val Glu Asp Ser Ala Leu Asp Leu Gln His Trp Glu Lys Glu Asp
50 55 60

ggc acc agc gtc att cct ttt ttc acc tcg tta gaa gca ctt caa cag
Gly Thr Ser Val Ile Pro Phe Phe Thr Ser Leu Glu Ala Leu Gln Gln
65 70 75 80

gcg gtt gaa gac gaa cag gca ttt gtc gta atg ccc gtt cgc acg ctg 288
Ala Val Glu Asp Glu Gln Ala Phe Val Val Met Pro Val Arg Thr Leu
85 90 95

ttt gag atg aca ctt ggc gaa acg ctc ttc ctt aat gcc aaa ctg cca 336
Phe Glu Met Thr Leu Gly Glu Thr Leu Phe Leu Asn Ala Lys Leu Pro

acc ggt aaa gaa ttt atg ccg cgt gaa atc agt ttg ttg att ggt gaa 384
Thr Gly Lys Glu Phe Met Pro Arg Glu Ile Ser Leu Leu Ile Gly Glu
115

gag gga aat ccg ctg agc agc cag gaa atc ctg gaa ggc ggt gaa tcg 432 Glu Gly Asn Pro Leu Ser Ser Gln Glu Ile Leu Glu Gly Gly Glu Ser 130 135 140

ctg ata tta tcg gaa gtc gca gag ccg cca gca caa atg att gat tca 480 Leu Ile Leu Ser Glu Val Ala Glu Pro Pro Ala Gln Met Ile Asp Ser 145 150 155 160

ctc acc acc tta ttt aaa acc att aag ccg gtg aag cgt gct ttt att 528 Leu Thr Thr Leu Phe Lys Thr Ile Lys Pro Val Lys Arg Ala Phe Ile

tgt tca att aaa gag aac gaa gag gca cag cct aat tta ctt att ggc 576 Cys Ser Ile Lys Glu Asn Glu Glu Ala Gln Pro Asn Leu Leu Ile Gly

att gaa gcc gat ggt gat atc gaa gaa att att cag gcg acg gga agt 624 Ile Glu Ala Asp Gly Asp Ile Glu Glu Ile Ile Gln Ala Thr Gly Ser 195 200 205

gta gcg acc gat aca tta cct ggc gat gaa cca atc gat att tgt cag 672 Val Ala Thr Asp Thr Leu Pro Gly Asp Glu Pro Ile Asp Ile Cys Gln

215 220 210 gtq aaa aaa ggg gaa aaa gga att agc cac ttt att acc gaa cat att Val Lys Lys Gly Glu Lys Gly Ile Ser His Phe Ile Thr Glu His Ile 230 235 geg eea tte tat gaa egt ege tgg ggt ggt ttt ttg egt gae ttt aaa Ala Pro Phe Tyr Glu Arg Arg Trp Gly Gly Phe Leu Arg Asp Phe Lys 245 250 cag aat cgg ata atc taa 786 Gln Asn Arq Ile Ile * 260 <210> 207 <211> 1266 <212> DNA <213> Escherichia coli <220> <221> CDS <222> (1)...(1266) <400> 207 atg ctc acg aaa aag aaa tgg gcg tta ttt agt cta tta aca ctg tgt Met Leu Thr Lys Lys Lys Trp Ala Leu Phe Ser Leu Leu Thr Leu Cys ggc ggt aca att tat aaa tta ccg tcg ctg aaa gat gcg ttt tat atc Gly Gly Thr Ile Tyr Lys Leu Pro Ser Leu Lys Asp Ala Phe Tyr Ile ccq atg cag gaa tat ttc cat ttg acc aat ggt caa att ggt aat gct Pro Met Gln Glu Tyr Phe His Leu Thr Asn Gly Gln Ile Gly Asn Ala 40 atg teg gta aac tea ttt gte ace aca gtg gge ttt ttt etg tet att 192 Met Ser Val Asn Ser Phe Val Thr Thr Val Gly Phe Phe Leu Ser Ile 55 tat ttt gcc gat aaa cta ccg cgc aga tac acc atg tca ttc tca ctc 240 Tyr Phe Ala Asp Lys Leu Pro Arg Arg Tyr Thr Met Ser Phe Ser Leu 65 att gcg aca gga tta ctg ggt gtt tat ttg acg aca atg ccg ggg tat 288 Ile Ala Thr Gly Leu Leu Gly Val Tyr Leu Thr Thr Met Pro Gly Tyr 85 tgg ggc atc ctc ttt gtc tgg gcg cta ttt ggc gtt act tgc gac atg 336 Trp Gly Ile Leu Phe Val Trp Ala Leu Phe Gly Val Thr Cys Asp Met 100 atg aac tgg ccg gtc ttg ctc aag tcg gta agt cga ttg ggc aat agc 384 Met Asn Trp Pro Val Leu Leu Lys Ser Val Ser Arg Leu Gly Asn Ser 115 120 gaa caa ggt cgg ttg ttt ggc ttc ttc gaa aca ggg cgt ggc att 432 Glu Gln Gln Gly Arg Leu Phe Gly Phe Phe Glu Thr Gly Arg Gly Ile

135

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	agt Ser							_								528
	gtg Val															576
	gag Glu															∙624
	acc Thr 210															672
	ttt Phe															720
	att Ile															768
	gct Ala								_	_		_				816
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	cta Leu 290															912
Ile 305		Leu	Pro	His	Glu 310	Ser	Met	Pro	Val	Tyr 315	Leu	Gly	Met	Ala	Cys 320	960
Thr	ctg Leu	Gly	Phe	Gly 325	Ala	Ile	Val	Phe	Thr 330	Gln	Arg	Ala	Val	Phe 335	Phe	1008
Ala	cct Pro	Ile	Gly 340	Glu	Ala	Lys	Ile	Ala 345	Glu	Asn	Lys	Thr	Gly 350	Ala	Ala	1056
	gcg Ala															1104
	ctg Leu 370															1152
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Lys Ile Val Phe Gly Ile Met Ala Cys Phe Ala Phe Ser Gly Ala Val gtt tcc gta atg ctg gtt aag cgt att agc caa cgt aag aaa gag atg 1248 Val Ser Val Met Leu Val Lys Arg Ile Ser Gln Arg Lys Lys Glu Met ctg geg get gaa get taa 1266 Leu Ala Ala Glu Ala * 420 <210> 208 <211> 2313 <212> DNA <213> Escherichia coli <220> <221> CDS <222> (1) ... (2313) <400> 208 atg cct cgc ttg tta acc aaa cgc ggc tgc tgg ata acg ttg gca gcc 48 Met Pro Arg Leu Leu Thr Lys Arg Gly Cys Trp Ile Thr Leu Ala Ala gcg ccc ttt ctc ctt ttt ctt gca gcg tgg gga gca gat aaa ctc tgg 96 Ala Pro Phe Leu Leu Phe Leu Ala Ala Trp Gly Ala Asp Lys Leu Trp cet eta ceg etg cat gaa gte aat eec gea ega gtg gte gtg geg eag Pro Leu Pro Leu His Glu Val Asn Pro Ala Arg Val Val Val Ala Gln gat ggt acg ccg ctc tgg cgc ttc gcc gat gct gac ggc atc tgg cgt 192 Asp Gly Thr Pro Leu Trp Arg Phe Ala Asp Ala Asp Gly Ile Trp Arg tat ccq qta aca atc gaa gat gtt tct cca cgt tac ctt gaa gcg ctg 240 Tyr Pro Val Thr Ile Glu Asp Val Ser Pro Arg Tyr Leu Glu Ala Leu 65 70 atc aat tat gaa gat ege tgg ttc tgg aag cat eeg ggg gtg aat eea 288 Ile Asn Tyr Glu Asp Arg Trp Phe Trp Lys His Pro Gly Val Asn Pro 85 ttc tcg gtg gcg cgc gca gca tgg caa gat ctc act tcg gga cgg gtt 336 Phe Ser Val Ala Arg Ala Ala Trp Gln Asp Leu Thr Ser Gly Arg Val 105 100 att tee ggt gge age aeg ete act atg eag gtt get egt etg ett gat 384 Ile Ser Gly Gly Ser Thr Leu Thr Met Gln Val Ala Arg Leu Leu Asp 120 115 cet cae ece aaa aca ttt gge gge aaa att ege eag ete tgg ege geg 432 Pro His Pro Lys Thr Phe Gly Gly Lys Ile Arg Gln Leu Trp Arg Ala 130 135 ttg caa ctg gaa tgg cat ctg tct aag cgt gaa att ctg acc ttg tat 480 Leu Gln Leu Glu Trp His Leu Ser Lys Arg Glu Ile Leu Thr Leu Tyr 145 150 155

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										aat Asn						576
										ccc Pro						624
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										gag Glu 235						720
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														ccg Pro 575		1728
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Val Ala Ala Asp Cys Pro Gln Ala Arg Gln Glu Met Ile Asn Val Trp 645 655	
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ggc	gtg Val	aaa Lys	aaa Lys 660	gcc Ala	gtg <b>V</b> al	tcg Ser	ggc	ttg Leu 665	cag Gln	gtg Val	cgc Arg	ctg Leu	att Ile 670	cgc Arg	gaa Glu	2016
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gtg Val	cga Arg	ccc Pro 755	qaA	cgt Arg	gtc Val	acg Thr	ctg Leu 760	Lys	ctg Leu	gat Asp	aaa Lys	gcc Ala 765	agt Ser	tat Tyr	cgc Arg	2304
cct Pro	ggc Gly 770	Asp	acc Thr	att Ile	aag Lys	ttg Leu 775	His	ato	gcc	gcg Ala	cca Pro 780	Thr	gcg Ala	Gly	aaa Lys	2352
ggt Gly	tat Tyr	gcg	atg Met	gtc Val	gag Glu	tcc Ser	agt Ser	gaa Glu	ggg Gly	ccg Pro	ctg Leu	tgg Trp	tgg Trp	caa Gln	gag Glu	2400

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tac ggc tgt ctt gag caa acc gcc agc ggc ctg ttt ccg tca ctt ta Tyr Gly Cys Leu Glu Gln Thr Ala Ser Gly Leu Phe Pro Ser Leu Ty 1185 1190 1195 12	r
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	gcc Ala															288
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	acc Thr		_	_					•	_		_		_	_	384
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	230	235	240
		tat cgg gtg gtt tcg c Tyr Arg Val Val Ser ( 255	
		cat atg gca agt gac a His Met Ala Ser Asp : 270	
		ttg ctg gcg cag gac g Leu Leu Ala Gln Asp G 285	
		gag tat gtg tta ttc of Glu Tyr Val Leu Phe 1 300	
aat ccg ttg gta gcg Asn Pro Leu Val Ala 305	ttg gga tta cgc gcg Leu Gly Leu Arg Ala 310	gga tta atg ctc gaa a Gly Leu Met Leu Glu I 315	aaa 960 Lys 320
ata agc taa Ile Ser *			969
<210> 212 <211> 1344 <212> DNA <213> Escherichia co	oli		
<220> <221> CDS <222> (1) (1344)			
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<221> CDS <222> (1)(1344) <400> 212 atg aac gcc tgg gaa Met Asn Ala Trp Glu 1 5 cat tac gcg ggc ctg	Val Asn Phe Asp Gly 10 tcg ttt ggt aat gaa	Leu Val Gly Leu Thr E	is egt 96
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<pre>&lt;221&gt; CDS &lt;222&gt; (1)(1344)  &lt;400&gt; 212 atg aac gcc tgg gaa Met Asn Ala Trp Glu 1</pre>	Val Asn Phe Asp Gly 10  tcg ttt ggt aat gaa Ser Phe Gly Asn Glu 25  ccg cga ctg gcg gcg Pro Arg Leu Ala Ala 40  gat gcg gga ttc ccc Asp Ala Gly Phe Pro 55  att ccg gtg ctg cgt	Leu Val Gly Leu Thr E 15  gcc tct acc cgt cac c Ala Ser Thr Arg His A 30  aag cag ggc tta ctg a Lys Gln Gly Leu Leu Leu L 45  cag gcc gtg atc ccg c Gln Ala Val Ile Pro E	egt 96 Arg Laa 144 Lys ecg 192 Pro

			gtc Val 100													336
			cca Pro													384
			ctg Leu													432
			ctg Leu													480
			gcg Ala													528
gca Ala	aac Asn	cac His	aat Asn 180	cgt Arg	ctc Leu	ggc Gly	ggt Gly	cat His 185	tac Tyr	ggt Gly	gaa Glu	ccg Pro	ggt Gly 190	atg Met	caa Gln	576 ·
			tac Tyr													624
			cga Arg													672
			aat Asn													720
			cag Gln													768
cgc Arg	cag Gln	gtg Val	ctg Leu 260	ttt Phe	tgc Cys	cac His	caa Gln	cag Gln 265	gcg Ala	ttc Phe	gct Ala	ċgc Arg	cag Gln 270	tca Ser	cag Gln	816
			aac Asn													864
			act Thr													912
			caa Gln													960
ctg Leu	cct Pro	cag Gln	gag Glu	tgt Cys 325	cgg Arg	gaa Glu	cac His	gcc Ala	gga Gly 330	gta Val	tgg Trp	ggt Gly	tat Tyr	ctc Leu 335	aat Asn	1008
gaa	ctc	ctt	gcc	gct	gac	aac	ccg	att	agc	gaa	cta	aaa	gtc	ttt	gat	1056

Glu Leu Leu Ala 340	Ala Asp	Asn Pro	Ile Ser 345	Glu Leu	-	Val :	Phe	Asp	
tta cgt gaa agc Leu Arg Glu Ser 355									1104
cgg gtg gta ttg Arg Val Val Leu 370	Thr Glu					_			1152
atg atg aac gat Met Met Asn Asp 385				_			_	_	1200
tac tac cgc gat Tyr Tyr Arg Asp						Pro (			1248
ctg cgc gaa ggg Leu Arg Glu Gly 420			_		Gln 1		_		1296
ctc ggt tcg gtt Leu Gly Ser Val 435									1344
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<pre>&lt;211&gt; 1479 &lt;212&gt; DNA &lt;213&gt; Escherich &lt;220&gt; &lt;221&gt; CDS &lt;222&gt; (1)(14 &lt;400&gt; 213 atg act tta tgg Met Thr Leu Trp 1 cgt gtg aag cgt Arg Val Lys Arg</pre>	att aac g Ile Asn G 5 aat ccg g Asn Pro G	Gly Asp gta tcg Val Ser gtc gag	Trp Ile 10 ggc gag Gly Glu 25 cag gct	Thr Gly gtg tta Val Leu tgt cgg	tgg of Trp of	caa g Gln G 30	Ala 15 ggc Gly	Ser aat Asn gcg	
<pre>&lt;211&gt; 1479 &lt;212&gt; DNA &lt;213&gt; Escherich &lt;220&gt; &lt;221&gt; CDS &lt;222&gt; (1)(14 &lt;400&gt; 213 atg act tta tgg Met Thr Leu Trp 1 cgt gtg aag cgt Arg Val Lys Arg 20 gat gcc gat gcc Asp Ala Asp Ala</pre>	att aac g Ile Asn ( 5 aat ccg g Asn Pro ( gct cag g Ala Gln (	gta tcg gta tcg Val Ser gtc gag Val Glu 40 cgg ctt	Trp Ile 10 ggc gag Gly Glu 25 cag gct Gln Ala tca ttt	Thr Gly gtg tta Val Leu tgt cgg Cys Arg gct gaa	tgg con trop of Ala A	caa g Gln G 30 gcc G Ala A	Ala 15 ggc Gly cgt Arg	ser aat Asn gcg Ala gtt	96
<pre>&lt;211&gt; 1479 &lt;212&gt; DNA &lt;213&gt; Escherich &lt;220&gt; &lt;221&gt; CDS &lt;222&gt; (1)(14 &lt;400&gt; 213 atg act tta tgg Met Thr Leu Trp 1  cgt gtg aag cgt Arg Val Lys Arg</pre>	att aac g Ile Asn ( 5 aat ccg g Asn Pro ( gct cag g Ala Gln ( tgg gcg g Trp Ala ( gcc gca ( gcc gca (	gta tcg yal Ser gtc gag yal Glu 40 cgg ctt Arg Leu 55	Trp Ile 10 ggc gag Gly Glu 25 cag gct Gln Ala tca ttt Ser Phe gaa agc	Thr Gly gtg tta Val Leu tgt cgg Cys Arg gct gaa Ala Glu 60 aat aaa	tgg of Trp of State of the Stat	caa g Gln ( 30) gcc ( Ala i cat g	Ala 15 ggc Gly cgt Arg gcc Ala	aat Asn gcg Ala gtt Val	96

85 90 95

				65					70					,,,		
	gtg Val															336
	gtt Val															384
	ctg Leu 130															432
	ttc Phe															480
	ggt Gly															528
	gaa Glu															576
	ctg Leu															624
	ctg Leu 210															672
	tac Tyr															720
	ctt Leu															768
gat Asp	atc Ile	gac Asp	gcg Ala 260	gct Ala	gtc Val	cat His	ctg Leu	acc Thr 265	att Ile	cag Gln	tcg Ser	gcg Ala	ttt Phe 270	gtc Val	aca Thr	816
	ggt Gly															864
	cag Gln 290															912
	acg Thr															960
	att Ile															1008

ctg gaa gcg atg Leu Glu Ala Met 340		_	Ala Pro Arg L		1056
gca ggg aca tcg Ala Gly Thr Ser 355					1104
gct ggc gta cca Ala Gly Val Pro 370					1152
cgt tat gat act Arg Tyr Asp Thr 385				-	1200
ttc gga ctc tct Phe Gly Leu Ser					1248
caa ctg ttg ctg Gln Leu Leu Leu 420			Val Asn Trp As		1296
ctt acc ggt gct Leu Thr Gly Ala 435					1344
ggt aac cat cgc Gly Asn His Arg 450					1392
ccg atg gcg agc Pro Met Ala Ser 465				_	1440
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Glu	Ala	Thr 35	Leu	Ser	Ala	Arg	Ile 40	Glu	Arg	Ala	Ile	Lys 45	Thr	Trp	Gln	
ggc	gaa Glu 50	ctg Leu	ccc Pro	aaa Lys	agt Ser	gag Glu 55	cag Gln	Gly	tat Tyr	gtg Val	ttc Phe 60	gtg Val	ctg Leu	gaa Glu	gat Asp	192
agc Ser 65	gag Glu	aca Thr	ggc	acc Thr	gtg Val 70	gcg Ala	Gly Gly	att Ile	tgt Cys	gcc Ala 75	att Ile	gag Glu	gtg Val	gcg Ala	gtt Val 80	240
					tgg Trp											288
					aat Asn											336
					ggc Gly											384
_	_		_		gag Glu					_	_			_	_	432
					gct Ala 150											480
					gtg Val											528
					cgc Arg											576
			100					103							•	
			ggc		gly aaa			gca					ctg			624
Phe	Leu	Cys 195 ccg	ggc Gly atc	Thr		Gln cac	Lys 200 ttt	gca Ala tta	Phe tcc	Ile cag	Ala	Glu 205 gcc	ctg Leu cag	Met	Pro	624 672
Phe aaa Lys atc	cat His 210	Cys 195 ccg Pro	ggc Gly atc Ile	Thr tat Tyr cat	Gly	Gln cac His 215 caa	Lys 200 ttt Phe	gca Ala tta Leu	Phe tcc Ser	Ile cag Gln gcc	Ala gaa Glu 220 cgc	Glu 205 gcc Ala gcg	ctg Leu cag Gln	Met gac Asp	Pro gtc Val	
Phe aaa Lys atc Ile 225	cat His 210 ggt Gly	Cys 195 ccg Pro cag Gln	ggc Gly atc Ile gta Val	Thr tat Tyr cat His	Gly acc Thr ccg Pro	cac His 215 caa Gln	Lys 200 ttt Phe acc Thr	gca Ala tta Leu gcg Ala	tcc ser cct Pro	cag Gln gcc Ala 235 gac	Ala gaa Glu 220 cgc Arg	Glu 205 gcc Ala gcg Ala	ctg Leu cag Gln gtg Val	Met gac Asp ctg Leu ggt	gtc Val gag Glu 240	672
Phe aaa Lys atc Ile 225 aaa Lys	cat His 210 ggt Gly gaa Glu acg	Cys 195 ccg Pro cag Gln ggt Gly	ggc Gly atc Ile gta Val ttt Phe	tat Tyr cat His cgc Arg 245	Gly acc Thr ccg Pro 230 tac	cac His 215 caa Gln cgt Arg	Lys 200 ttt Phe acc Thr aac Asn	gca Ala tta Leu gcg Ala tat Tyr	Phe tcc Ser cct Pro atc Ile 250	cag Gln gcc Ala 235 gac Asp	Ala gaa Glu 220 cgc Arg atc Ile	Glu 205 gcc Ala gcg Ala ttt Phe	ctg Leu cag Gln gtg Val gac Asp	Met gac Asp ctg Leu ggt Gly 255	gtc Val gag Glu 240 ggg Gly	672 720

275 280 285 ged tge etg gtd gdd aat gaa aat tat dad dat tte egd gtg gtg etg Ala Cys Leu Val Ala Asn Glu Asn Tyr His His Phe Arg Val Val Leu 290 295 gtg cgt acc gat ccg gca acc gag cgt ttg att tta acc gcc gca caa 960 Val Arg Thr Asp Pro Ala Thr Glu Arg Leu Ile Leu Thr Ala Ala Gln 305 310 ctg gat gcc ctc aaa tgc cac gcc ggg gat cgc gtt cgt ctg gtg cgc 1008 Leu Asp Ala Leu Lys Cys His Ala Gly Asp Arg Val Arg Leu Val Arg 325 330 ctg tgc gca gag gag aaa aca gca tga 1035 Leu Cys Ala Glu Glu Lys Thr Ala * <210> 215 <211> 1221 <212> DNA <213> Escherichia coli <220> <221> CDS <222> (1)...(1221) atg tot cag cca att acg cgt gaa aac ttt gat gaa tgg atg ata cct Met Ser Gln Pro Ile Thr Arg Glu Asn Phe Asp Glu Trp Met Ile Pro gtt tac gct ccg gca ccc ttt ata ccg gta cgt ggc gaa ggt tcg cgc Val Tyr Ala Pro Ala Pro Phe Ile Pro Val Arg Gly Glu Gly Ser Arg ttg tgg gat cag cag ggg aaa gag tat atc gac ttc gcg ggt ggc att 144 Leu Trp Asp Gln Gln Gly Lys Glu Tyr Ile Asp Phe Ala Gly Gly Ile geg gtg aac geg ctg ggc cat geg cat ceg gaa ctg cgt gaa geg ctg 192 Ala Val Asn Ala Leu Gly His Ala His Pro Glu Leu Arg Glu Ala Leu aac gaa cag gcg agt aag ttc tgg cat acc ggc aac ggt tac acc aac Asn Glu Gln Ala Ser Lys Phe Trp His Thr Gly Asn Gly Tyr Thr Asn gag eeg gta etg ega etg geg aaa aaa ttg ate gae gee aeg ttt gee 288 Glu Pro Val Leu Arg Leu Ala Lys Lys Leu Ile Asp Ala Thr Phe Ala 85 gat ege gtc ttc ttt tgt aac tee ggt geg gaa gee aac gaa geg geg 336 Asp Arg Val Phe Phe Cys Asn Ser Gly Ala Glu Ala Asn Glu Ala Ala 100 105 cta aaa ctg gcg cgt aaa ttc gct cac gac cgc tac ggc agc cat aag

Leu Lys Leu Ala Arg Lys Phe Ala His Asp Arg Tyr Gly Ser His Lys
115 120 125

	Ile Val	gcg tto Ala Phe										432
		ggt ggg Gly Gly 150	Gln Pr									480
		att cgt Ile Arg 165										528
		gac gac Asp Asp										576
		ggt gtg Gly Val		o Ala								624
	Glu Lev	r tgt aac . Cys Asr										672
		gtc ggg Val Gly 230	Arg Th									720
tac ggo Tyr Gly	gtg acg Val Thi	cct gat Pro Asp 245	ctg tt Leu Le	a act u Thr	acc Thr 250	gcc Ala	aaa Lys	gcg Ala	ctg Leu	ggc Gly 255	ggc Gly	768
		ggt gcg Gly Ala										816
		act cat		r Thr								864
tcg gcg Ser Ala 290	Val Ala	ggc aaa Gly Lys	gtg ct Val Le 295	g gag u Glu	ctc Leu	Ile	aac Asn 300	Thr	cca Pro	gag Glu	atg Met	912
		aaa cag Lys Glr 310	Arg Hi									960
		e ege tat s Arg Tyr 325										
		tgt gta 7 Cys Val )										1056
		g gaa gco n Glu Ala		s Ala								1104
ggt ggd	aac gt	g gtg cgt	ttt go	g cct	gcg	ctc	aat	gtc	agc	gaa	gaa	1152

Gly Gly Asn Val Val Arg Phe Ala Pro Ala Leu Asn Val Ser Glu Glu 375 gag gtg acg acc gga ctg gat cgc ttt gca gct tgc gaa cac ttt 1200 Glu Val Thr Thr Gly Leu Asp Arg Phe Ala Ala Ala Cys Glu His Phe gtt agc cga ggt tca tca tga 1221 Val Ser Arg Gly Ser Ser * 405 <210> 216 <211> 3147 <212> DNA <213> Escherichia coli <220> <221> CDS <222> (1)...(3147) <400> 216 atg aaa att ctc agc ctg cgc ctg aaa aac ctg aac tca tta aaa ggc Met Lys Ile Leu Ser Leu Arg Leu Lys Asn Leu Asn Ser Leu Lys Gly gaa tgg aag att gat ttc acc cgc gag ccg ttc gcc agc aac ggg ctg Glu Trp Lys Ile Asp Phe Thr Arg Glu Pro Phe Ala Ser Asn Gly Leu 20 25 ttt get att acc ggc cca aca ggt geg ggg aaa acc acc ctg ctg gac 144 Phe Ala Ile Thr Gly Pro Thr Gly Ala Gly Lys Thr Thr Leu Leu Asp gcc att tgt ctg gcg ctg tat cac gaa act ccg cgt ctc tct aac gtt 192 . Ala Ile Cys Leu Ala Leu Tyr His Glu Thr Pro Arg Leu Ser Asn Val tca caa tcg caa aat gat ctc atg acc cgc gat acc gcc gaa tgt ctg 240 Ser Gln Ser Gln Asn Asp Leu Met Thr Arg Asp Thr Ala Glu Cys Leu 65 gcg gag gtg gag ttt gaa gtg aaa ggt gaa gcg tac cgt gca ttc tgg Ala Glu Val Glu Phe Glu Val Lys Gly Glu Ala Tyr Arg Ala Phe Trp age cag aat egg geg egt aac caa eee gae ggt aat ttg cag gtg eea 336 Ser Gln Asn Arg Ala Arg Asn Gln Pro Asp Gly Asn Leu Gln Val Pro 100 105 cgc gta gag ctg gcg cgc tgc gcc gac ggc aaa att ctc gcc gac aaa 384 Arg Val Glu Leu Ala Arg Cys Ala Asp Gly Lys Ile Leu Ala Asp Lys 115 120 gtg aaa gat aag ctg gaa ctg aca gcg acg tta acc ggg ctg gat tac 432 Val Lys Asp Lys Leu Glu Leu Thr Ala Thr Leu Thr Gly Leu Asp Tyr 130 135 ggg ege tte acc egt teg atg etg ett teg eag ggg eaa ttt get gee Gly Arg Phe Thr Arg Ser Met Leu Leu Ser Gln Gly Gln Phe Ala Ala 145 150 155

					ccc Pro											528
			_		tac Tyr				_		_	_			_	576
		_	_	_	aca Thr		_		_	_			_	_	-	624
					acg Thr											672
_	_	_			gac Asp 230	_	_		_					_	_	720
	_			_	cta Leu				_	_	_	_	-	_	_	768
					cgt Arg											816
					cct Pro											864
					cca Pro											912
_	_				ege Arg 310	_	_		_	_	-			_		960
-	_				ctt Leu	-		-		_					_	1008
_		_	_		cag Gln	_	_			-	_					1056
					ttc Phe											1104
					caa Gln											1152
					acc Thr 390											1200

	cg ttg acg hr Leu Thr 405		_		_		-	1248
	ct gag caa la Glu Gln 420							1296
Gly Gln I	tt gtt ccc le Val Pro 35							1344
_	at gtc acg sn Val Thr	_	-	-	_	-		1392
	gc cag cgt rg Gln Arg							1440
	tt tgc gag Ie Cys Glu 485							1488
	ag tta cag ln Leu Gln 500							1536
Ser His P	eg geg gte ro Ala Val 15		_					1584
	ga tta ctg rg Leu Leu							1632
	eg acg cta la Thr Leu		_			-		1680
	at gaa aac sp Glu Asn 565	Glu Ala	Gln Ser					1728
	aa caa tgg In Gln Trp 580	_		_			-	1776
Gln Pro Le	tg gac gat eu Asp Asp 95				_			1824
	ag ctg cgg Ln Leu Arg							1872
att gcc gc Ile Ala Al 625	eg cat aat la His Asn	cag caa Gln Gln 630	att atc Ile Ile	cag tat Gln Tyr 635	caa cag Gln Gln	caa att Gln Ile	gaa 1 Glu 640	1920
caa cgc ca	ag caa cta	ctt tta	acg aca	ttg acg	ggt tat	gca ctg	aca :	1968

Gln	Arg	Gln	Gln	Leu 645	Leu	Leu	Thr	Thr	Leu 650	Thr	Gly	Tyr	Ala	Leu 655	Thr	
			gaa Glu 660													2016
_	-	_	agc Ser		_		_	_		_				_		2064
	-		cag Gln	_		_	_		_	_	_	-	_		_	2112
_	_		ccg Pro		_	_	_			_	_	_				2160
-	-		gaa Glu		_					_	_	_	_	_		2208
_		_	gat Asp 740	-	-				_	_			_		_	2256
_		_	acc Thr			_	-	-	_		_	_	_	_		2304
			gcg Ala		_	_	_				_	_	_	_	_	2352
	_	_	aat Asn	_	_		_	_	_	_				_	_	2400:
	_		gca Ala	-	_	_	-	_					_		_	2448
			gct Ala 820													2496
			cac His		_	_	_	_			_	_				2544
			cag Gln													2592
			cag Gln													2640
			aat Asn													2688

885 890 895 aag ttt gee cag ggg etg aeg etg gat aat tta gte eat ete get aat 2736 Lys Phe Ala Gln Gly Leu Thr Leu Asp Asn Leu Val His Leu Ala Asn cag caa ctt acc cgg ctg cac ggg cgc tat ctg tta cag cgc aaa gcc 2784 Gln Gln Leu Thr Arg Leu His Gly Arg Tyr Leu Leu Gln Arg Lys Ala age gag geg etg gaa gte gag gtt gtt gat ace tgg cag gca gat geg 2832 Ser Glu Ala Leu Glu Val Glu Val Val Asp Thr Trp Gln Ala Asp Ala 930 gta cgc gat acc cgt acc ctt tcc ggc ggc gaa agt ttc ctc gtt agt 2880 Val Arg Asp Thr Arg Thr Leu Ser Gly Glu Ser Phe Leu Val Ser 945 950 ctg gcg ctg gcg ctg gcg ctt tcg gat ctg gtc agc cat aaa aca cgt 2928 Leu Ala Leu Ala Leu Ser Asp Leu Val Ser His Lys Thr Arg 965 970 att gac teg etg tte ett gat gaa ggt ttt gge aeg etg gat age gaa 2976 Ile Asp Ser Leu Phe Leu Asp Glu Gly Phe Gly Thr Leu Asp Ser Glu 980 acg ctg gat acc gcc ctt gat gcg ctg gat gcc ctg aac gcc agt ggc 3024 Thr Leu Asp Thr Ala Leu Asp Ala Leu Asp Ala Leu Asn Ala Ser Gly 995 1000 aaa acc atc ggt gtg att agc cac gta gaa gcg atg aaa gag cgt att 3072 Lys Thr Ile Gly Val Ile Ser His Val Glu Ala Met Lys Glu Arg Ile 1010 1015 ccg gtg cag atc aaa gtg aaa aag atc aac ggc ctg ggc tac agc aaa 3120 Pro Val Gln Ile Lys Val Lys Lys Ile Asn Gly Leu Gly Tyr Ser Lys 1025 1030 1035 ctg gaa agt acg ttt gca gtg aaa taa 3147 Leu Glu Ser Thr Phe Ala Val Lys * 1045 <210> 217 <211> 1203 <212> DNA <213> Escherichia coli <220> <221> CDS <222> (1) ... (1203) <400> 217 atg ege ate ett cae ace tea gae tgg eat ete gge eag aae tte tae Met Arg Ile Leu His Thr Ser Asp Trp His Leu Gly Gln Asn Phe Tyr 5 agt aaa agc cgc gaa gct gaa cat cag gct ttt ctt gac tgg ctg ctg Ser Lys Ser Arg Glu Ala Glu His Gln Ala Phe Leu Asp Trp Leu Leu

				acc Thr												144
				ggc Gly												192
				aat Asn												240
				gac Asp 85												288
				aat Asn												336
		_		cgt Arg	-	_		_			_		_	_		384
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90	-			cgt Arg	_		_	_		_	-			_	_	384
				gtt Val												432
				gtg Val												480
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_				_			_	_						tta Leu	_	816
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				ctt Leu 245												768
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_	_	_	_					-		gtt Val					-	528 ·
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-222-

<213> Escherichia coli

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225	egc ttt Arg Phe	aat cag Asn Glr 230	ctt a Leu 1	atc ctc Ile Leu	gag ac Glu Th 235	g gct r Ala	ggc Gly	gta Val	ccg Pro 240	720
caa act gtc Gln Thr Val				_			_		_	768
gcg ctg gtg Ala Leu Val		_	Gln A				_	_	_	816
ttt ggc aaa Phe Gly Lys 275										864
aac tac tcc Asn Tyr Ser 290			Gly G			u Thr				912
ttg ctg aca Leu Leu Thr 305										960
gga agc ttt Gly Ser Phe										1008
gct atg ccg Ala Met Pro			Leu I		tga *					1041
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<pre>&lt;211&gt; 1356 &lt;212&gt; DNA &lt;213&gt; Eschei &lt;220&gt; &lt;221&gt; CDS &lt;222&gt; (1) &lt;400&gt; 229 atg ttt tca Met Phe Ser 1 atg ctg ccg</pre>	gaa gtc Glu Val 5 att gtc Ile Val 20	atg cgt Met Arg atc att Ile Ile aaa gcg	att tile F	Ile Leu 10 ttt tct Phe Ser 25 ctg cat	Asp Le	u Gly a tta e Leu g att	ggc Gly 30	Thr 15 atg Met	Val aag Lys gtt	
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Ala Lys 65	Ala Met	Ala	Glu 70	Asn	Phe	Asp	Leu	Asn 75	Leu	His	Val	Val	Asp 80	
gtt ggc Val Gly														288
ctg gtg		Pro												336
acc cgt Thr Arg	-			-		_	_							384
atg acc Met Thr 130				_	_		_	-					_	432
ata ggg   Ile Gly   145				_				_		_		-		480
ggc gac Gly Asp		_	_	_		_					_	_		528
att gct Ile Ala		His												576
ctg gtc									_		_			624
ttt agc Phe Ser 210		_		_	_									672
gtc acc Val Thr 225														720
tac gat														768
atg ctg Met Leu		Pro												816
ccc atc Pro Ile														864
	275													
cag gag Gln Glu 290	ttc ctg													912

305	310	315	320
	Gly Asn Gln Val	ctg ccg ttt ggc gat ctt Leu Pro Phe Gly Asp Leu 330 335	
		gte gee gtg cat egt gga Val Ala Val His Arg Gly 350	
_		atc att atg agc atc acc Ile Ile Met Ser Ile Thr 365	-
		cac acc caa ctg gcg gct His Thr Gln Leu Ala Ala 380	
		gtg gct tca atg gat cag Val Ala Ser Met Asp Gln 395	
	Trp Leu Leu Ile	cag gtt ttc tcc ccg caa Gln Val Phe Ser Pro Gln 410 415	
		att tat ctg acc ggt att Ile Tyr Leu Thr Gly Ile 430	
		att aaa caa gag aaa gtc Ile Lys Gln Glu Lys Val 445	-
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		aat gaa ata gaa acc tat Asn Glu Ile Glu Thr Tyr 45	

gat ggt gtg cat ttg ata tgc acc act gcc aaa gtg gat cgt agt tt Asp Gly Val His Leu Ile Cys Thr Thr Ala Lys Val Asp Arg Ser Ph 50 55 60	
ggc gat att ccg tta gtt cac ggc atg cct ttt att tct ggt atc gg Gly Asp Ile Pro Leu Val His Gly Met Pro Phe Ile Ser Gly Ile Gl 65 70 75 8	
atc gaa gca tta caa aat aaa att ctg act atc tta cag ggg tga Ile Glu Ala Leu Gln Asn Lys Ile Leu Thr Ile Leu Gln Gly * 85 90	285
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gaa gtt tta acc cat atc ggt aat gag atg ctc gcc aaa ggt gtg gt Glu Val Leu Thr His Ile Gly Asn Glu Met Leu Ala Lys Gly Val Va 20 25 30	
cat gat acc tgg cca cag gca tta att gcc aga gaa gca gaa ttc cc His Asp Thr Trp Pro Gln Ala Leu Ile Ala Arg Glu Ala Glu Phe Pr 35 40 45	
acc ggg ata atg ctt gag cag cac gct att gca ata ccg cat tgt ga Thr Gly Ile Met Leu Glu Gln His Ala Ile Ala Ile Pro His Cys Gl 50 55 60	
gcg att cat gct aag tcg tca gcc att tat ctg tta agg cca aca aa Ala Ile His Ala Lys Ser Ser Ala Ile Tyr Leu Leu Arg Pro Thr As 65 70 75 8	n ,
aaa gtt cat ttt cag caa gcg gat gat gat aac gac gtg gcg gta tc Lys Val His Phe Gln Gln Ala Asp Asp Asp Asn Asp Val Ala Val Se 85 90 95	
ttg gtt att gcg ttg att gtg gaa aat ccg cag cag caa ttg aaa ct Leu Val Ile Ala Leu Ile Val Glu Asn Pro Gln Gln Gln Leu Lys Le 100 105 110	
tta cgc tgt tta ttt ggc aag tta caa cag ccc gat atc gtc gag ac Leu Arg Cys Leu Phe Gly Lys Leu Gln Gln Pro Asp Ile Val Glu Th 115 120 125	
cta atc act ctt cct gaa acc cag tta aag gaa tac ttc aca aag ta Leu Ile Thr Leu Pro Glu Thr Gln Leu Lys Glu Tyr Phe Thr Lys Ty 130 135 140	
gtt tta gat tca gac gaa taa	453

Val Leu Asp Ser Asp Glu * 150 <210> 232 <211> 1263 <212> DNA <213> Escherichia coli <220> <221> CDS <222> (1) ... (1263) <400> 232 atg aaa acg tta att gcc cgg cat aaa gct ggt gaa cat atc ggc ata Met Lys Thr Leu Ile Ala Arg His Lys Ala Gly Glu His Ile Gly Ile tgt tca gtc tgt tct gcc cat ccg ttg gtt atc gaa gcg gcg ctg gca 96 Cys Ser Val Cys Ser Ala His Pro Leu Val Ile Glu Ala Ala Leu Ala ttt gat cgc aac agc acg cgc aaa gtg ctg att gaa gca acg tca aac Phe Asp Arg Asn Ser Thr Arg Lys Val Leu Ile Glu Ala Thr Ser Asn 35 40 cag gtc aat caa ttt ggc ggt tat acc gga atg aca ccg gca gac ttt 192 Gln Val Asn Gln Phe Gly Gly Tyr Thr Gly Met Thr Pro Ala Asp Phe 50 55 ege gaa tit git tit aeg att gee gat aaa git ggg tit gea ege gaa 240 Arg Glu Phe Val Phe Thr Ile Ala Asp Lys Val Gly Phe Ala Arg Glu 70 ege att att ete gge gge gat eat etg ggg eea aac tge tgg eag eaa 288 Arg Ile Ile Leu Gly Gly Asp His Leu Gly Pro Asn Cys Trp Gln Gln gaa aat gcg gat gcg gcg atg gaa aaa tcc gtc gag ctg gta aag gaa Glu Asn Ala Asp Ala Ala Met Glu Lys Ser Val Glu Leu Val Lys Glu 105 tat gtt cgt gcc ggc ttc agt aaa att cat ctt gat gcg tca atg tcc 384 Tyr Val Arg Ala Gly Phe Ser Lys Ile His Leu Asp Ala Ser Met Ser 115 120 tgc gcg ggg gat ccc ata ccg tta gca cca gaa acg gtt gcg gaa cga 432 Cys Ala Gly Asp Pro Ile Pro Leu Ala Pro Glu Thr Val Ala Glu Arg 135 130 gct gct gtg ctt tgc ttt gct gcg gaa agt gtg gcg aca gat tgc cag 480 Ala Ala Val Leu Cys Phe Ala Ala Glu Ser Val Ala Thr Asp Cys Gln 145 cgt gag caa ctg age tat gtc att ggc acc gaa gtt ccg gtt ccg ggc 528 Arg Glu Gln Leu Ser Tyr Val Ile Gly Thr Glu Val Pro Val Pro Gly 165 170 ggt gag gcc agc gcc att cag tca gta cac atc acc cat gtt gaa gat 576 Gly Glu Ala Ser Ala Ile Gln Ser Val His Ile Thr His Val Glu Asp 180 185

gcc Ala																624
ctg Leu				tta Leu												672
gtg Val 225																720
				caa Gln 245												768
cat His				tac Tyr												816
gat Asp	cac His	ttt Phe 275	gca Ala	ata Ile	ttg Leu	aaa Lys	gtc Val 280	ggt Gly	ccc Pro	gca Ala	tta Leu	acc Thr 285	ttt Phe	gct Ala	tta Leu	864
				ttt Phe												912
				agc Ser												960
				tac Tyr 325												1008
				att Ile												1056
				cgg Arg		ГЛS										1104
				gac Asp												1152
				cgc Arg												1200
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195 200 205 ctg cat ggc gcg tca ggg tta tcg act aag gat att cag caa acc atc 672 Leu His Gly Ala Ser Gly Leu Ser Thr Lys Asp Ile Gln Gln Thr Ile 210 215 aaa ctg ggg ata tgc aaa atc aac gtt gca acg gag ctg aaa aat gcc 720 Lys Leu Gly Ile Cys Lys Ile Asn Val Ala Thr Glu Leu Lys Asn Ala ttc tcg cag gcg tta aaa aat tac ctg acc gag cac cct gaa gcg acc 768 Phe Ser Gln Ala Leu Lys Asn Tyr Leu Thr Glu His Pro Glu Ala Thr gat eec egg gat tat ttg eag teg get aaa tee gea atg ege gat gtg 816 Asp Pro Arg Asp Tyr Leu Gln Ser Ala Lys Ser Ala Met Arg Asp Val 260 265 gtg agc aaa gtg att gcc gat tgt ggc tgc gag ggc agg gca taa 861 Val Ser Lys Val Ile Ala Asp Cys Gly Cys Glu Gly Arg Ala * 280 <210> 234 <211> 474 <212> DNA <213> Escherichia coli <220> <221> CDS <222> (1)...(474) <400> 234 atg agt caa aac gat atc att atc aga act cat tat aag tct cct cat Met Ser Gln Asn Asp Ile Ile Ile Arg Thr His Tyr Lys Ser Pro His aga ttg cac atc gat agc gac ata cca aca cct tca tca gag cct att Arg Leu His Ile Asp Ser Asp Ile Pro Thr Pro Ser Ser Glu Pro Ile aat caa ttt gcg cgc cag ctc atc acc cta ctt gat acc tct gac tta 144 Asn Gln Phe Ala Arg Gln Leu Ile Thr Leu Leu Asp Thr Ser Asp Leu agt teg atg etg tea tac tgt gtt act cag gaa ttt acc gea aac tgt 192 Ser Ser Met Leu Ser Tyr Cys Val Thr Gln Glu Phe Thr Ala Asn Cys cga aaa ata tca caa aat tgt tat tcc act gcc ctt ttt acc att aac 240 Arg Lys Ile Ser Gln Asn Cys Tyr Ser Thr Ala Leu Phe Thr Ile Asn ttt gcc act tca ccc atc cat aca gaa aat ata ctc att aca tta cac 288 Phe Ala Thr Ser Pro Ile His Thr Glu Asn Ile Leu Ile Thr Leu His tat aaa aaa gaa atc att tcc tta tta ctg gaa acc acg cct att aaa

Tyr Lys Lys Glu Ile Ile Ser Leu Leu Leu Glu Thr Thr Pro Ile Lys

105

100

															•	
	aac Asn															384
	gct Ala 130															432
	gaa Glu															474
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	gcc Ala															96
	cat His															144
	gac Asp 50															192
	gtt Val															240
	cga Arg															288
	gac Asp															336
tat Tyr	gga Gly	caa Gln 115	tta Leu	aat Asn	tat Tyr	gtt Val	gtg Val 120	tcc Ser	gtt Val	tac Tyr	gac Asp	ccg Pro 125	aac Asn	gat Asp	acc Thr	384
	gtt Val 130															432

	gat Asp															480
_	tat Tyr	_	_		_	_		_		_						528
	gtt Val			_												576
•	cct Pro				_	_	_	_			_	_			_	624
	caa Gln 210	_							_	_					_	672
	gaa Glu			_					_		-	_				720
	tta Leu															768
	atg Met															816
_	aat Asn	_	_			_				_	-		_			864
	ctt Leu 290				_	_				_	_			_		912
	ctg Leu								Ala		Glu					960
	ctg Leu															1008
	tta Leu															1056
	ctc Leu															1104
_	aac Asn 370		_	_					_		_	_				1152
gca	tta	tac	atc	gcc	atg	agc	aag	ggt	aat	gaa	gac	gtc	gtg	tta	tct	1200

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cat cag tta ttt aca cta ttg gcc gct aaa aat cat gac aac atg tca His Gln Leu Phe Thr Leu Leu Ala Ala Lys Asn His Asp Asn Met Ser 420 425 430	1296
gct gtt cat ata gcc att cat cat aag cat tat aaa act gta gaa aca Ala Val His Ile Ala Ile His His Lys His Tyr Lys Thr Val Glu Thr 435 440 445	1344
tat tat gct gct att aat gca atc agc caa agc ctg agt ttt agt gct Tyr Tyr Ala Ala Ile Asn Ala Ile Ser Gln Ser Leu Ser Phe Ser Ala 450 455 460	1392
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atg cca tct gga tta ttt atg gac tta ttg cct ttt tta ctg gac gcg Met Pro Ser Gly Leu Phe Met Asp Leu Leu Pro Phe Leu Leu Asp Ala	48 96
atg cca tct gga tta ttt atg gac tta ttg cct ttt tta ctg gac gcg Met Pro Ser Gly Leu Phe Met Asp Leu Leu Pro Phe Leu Leu Asp Ala  1 5 10 15  aac ctc agc gcg aca aac cca ccc gct att ccg cac tgg tgg aag cgt Asn Leu Ser Ala Thr Asn Pro Pro Ala Ile Pro His Trp Trp Lys Arg	
atg cca tct gga tta ttt atg gac tta ttg cct ttt tta ctg gac gcg Met Pro Ser Gly Leu Phe Met Asp Leu Leu Pro Phe Leu Leu Asp Ala  1 5 10 15  aac ctc agc gcg aca aac cca ccc gct att ccg cac tgg tgg aag cgt Asn Leu Ser Ala Thr Asn Pro Pro Ala Ile Pro His Trp Trp Lys Arg  20 25 30  caa ccg ctt att ccc aac ctt ctg tca cag gaa ctg aaa aac tat ctg Gln Pro Leu Ile Pro Asn Leu Leu Ser Gln Glu Leu Lys Asn Tyr Leu	96
atg cca tct gga tta ttt atg gac tta ttg cct ttt tta ctg gac gcg Met Pro Ser Gly Leu Phe Met Asp Leu Leu Pro Phe Leu Leu Asp Ala  1 5 10 15  aac ctc agc gcg aca aac cca ccc gct att ccg cac tgg tgg aag cgt Asn Leu Ser Ala Thr Asn Pro Pro Ala Ile Pro His Trp Trp Lys Arg  20 25 30  caa ccg ctt att ccc aac ctt ctg tca cag gaa ctg aaa aac tat ctg Gln Pro Leu Ile Pro Asn Leu Leu Ser Gln Glu Leu Lys Asn Tyr Leu  35 40 45  aag ctt aat gtt aaa gag aaa aat att cag att gca gac cag gta att Lys Leu Asn Val Lys Glu Lys Asn Ile Gln Ile Ala Asp Gln Val Ile	96 144
atg cca tct gga tta ttt atg gac tta ttg cct ttt tta ctg gac gcg Met Pro Ser Gly Leu Phe Met Asp Leu Leu Pro Phe Leu Leu Asp Ala  1	96 144 192

ctt a					_	_	_	_	-			_			_	384
taa *																387
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ttt Phe		_	_		_	_			_		-			_		96
gac Asp																144
ctg :																192
aac Asn 65																240
cgc Arg																288
aaa Lys																336
gtt Val																384
atg Met																432
ggc Gly 145						_					_		_			480
cgc	gcg	acc	gta	aag	ttg	ccg	atg	att	gtt	atg	aag	cgc	acg	cta	cag	528

Arg	Ala	Thr	Val	Lys 165	Leu	Pro	Met	Ile	Val 170	Met	Lys	Arg	Thr	Leu 175	Gln	
	ctc Leu															576
	cgt Arg															624
	gaa Glu 210															672
	cgg Arg															720
_	egt Arg				_	_			_							768
_	tgt Cys	_	_	_			_				_	_				816
	agt Ser															864
	ctc Leu 290															912
	gtg Val															960
	ggt Gly	-		_	-				_	_		_	_			1008
	gcg Ala															1056
	att Ile															1104
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		-	_	-	cag Gln	_								_		672
_		-		-	tat Tyr 230	-		_			-	_	_			720
	_	-		-	tat Tyr	_	_					_		_	_	768
			_	_	tat Tyr		_		_					_		816
					Gly											864
_	_	_		_	gat Asp		_		_					_		912
	_	_			ctg Leu 310	-			_		_	_	_		-	960
			_		gag Glu	_		-		_	_	-			_	1008
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Thr Val Arg	agc ct Ser Le												1392
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aaa ccc gat Lys Pro Asp 515	Leu Al		_		-	_		_		_	-		1584
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330

335

325

aat gaa att aat caa cca tct gcg cca ggt gtt aat ttt gat gat att

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	ttg Leu															624
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	atc Ile															720
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	ccg Pro															816
	atc Ile				_		_			-		_	_		_	864
	ctg Leu 290															912
-	tcc Ser		_	-				_	_	_	_	_	_		_	960
	acc Thr															1008
	cgg Arg		_			_		-			_		_	_	_	1056
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<213> Escherichia coli

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					gta Val											768
					gcg Ala											816
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					aac Asn											912
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					aaa Lys											1008
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Ala					atg Met											1152
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					gat Asp											1296
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gcc	gga	aaa	gtg	ctt	gcc	agc	ggt	aca	ccg	cag	gaa	ctg	gtt	gag	aaa	1440

Ala 465	Gly	Lys	Val	Leu	Ala 470	Ser	Gly	Thr	Pro	Gln 475	Glu	Leu	Val	Glu	Lys 480	
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				gcg Ala												1872
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				cac His												2016
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				ctg Leu												2160

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	Pro Gly Arg		gag gtt tac ccg Glu Val Tyr Pro 845	_
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				gct Ala												144
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				gaa Glu 85												288
				gtt Val												336
				gcc Ala												384
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				tct Ser												480
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				gaa Glu												672
				cca Pro												720
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O.Lu	_		ggc Gly 260	_	_		_			_	_		-			816
			cca Pro													864
			cag Gln													912
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85 90 tgc tgg cag gac ggt gga cgt aaa aac tgc gct aaa gat ccg gtc tat Cys Trp Gln Asp Gly Gly Arg Lys Asn Cys Ala Lys Asp Pro Val Tyr ege aag atg gaa age gat atg cat aac etg eag eeg tea gte ggt gag Arg Lys Met Glu Ser Asp Met His Asn Leu Gln Pro Ser Val Gly Glu 120 gtg aat ggc gat cgc ggc aac ttt atg tac agc cag tgg aat ggc ggt Val Asn Gly Asp Arg Gly Asn Phe Met Tyr Ser Gln Trp Asn Gly Gly qaa ggc cag tac ggt caa tgc gcc atg aag gtc gat ttc aaa gaa aaa Glu Gly Gln Tyr Gly Gln Cys Ala Met Lys Val Asp Phe Lys Glu Lys get gee gaa eea eea geg egt gea ege ggt gee att geg ege ace tae Ala Ala Glu Pro Pro Ala Arg Ala Arg Gly Ala Ile Ala Arg Thr Tyr 170 576 tte tat atg ege gae caa tae aac etg aca ete tet ege cag caa aeg Phe Tyr Met Arg Asp Gln Tyr Asn Leu Thr Leu Ser Arg Gln Gln Thr 185 cag ctg ttc aac gca tgg aac aag atg tat ccg gtt acc gac tgg gag 624 Gln Leu Phe Asn Ala Trp Asn Lys Met Tyr Pro Val Thr Asp Trp Glu 200 tgc gag cgc gat gaa cgc atc gcg aag gtg cag ggc aat cat aac ccg 672 Cys Glu Arg Asp Glu Arg Ile Ala Lys Val Gln Gly Asn His Asn Pro 215 tat gtg caa cgc gct tgc cag gcg cga aag agc taa 708 . Tyr Val Gln Arg Ala Cys Gln Ala Arg Lys Ser 225 230 <210> 244 <211> 1443 <212> DNA <213> Escherichia coli <220> <221> CDS <222> (1) ... (1443) atg tee aga agg ett ege aga aca aaa ate gtt ace aeg tta gge eea Met Ser Arg Arg Leu Arg Arg Thr Lys Ile Val Thr Thr Leu Gly Pro 5 10 15 gca aca gat ege gat aat aat ett gaa aaa gtt ate geg geg ggt gee Ala Thr Asp Arg Asp Asn Asn Leu Glu Lys Val Ile Ala Ala Gly Ala 20 25 aac gtt gta cgt atg aac ttt tct cac ggc tcg cct gaa gat cac aaa 144 Asn Val Val Arg Met Asn Phe Ser His Gly Ser Pro Glu Asp His Lys

35

	cgc Arg 50															192
	gct Ala															240
	aaa Lys															288
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					aac Asn											192
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		_	_		gcg Ala	-	_	_	_		_		_	_	_	288
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atc	σσa	cta	att	aac	acc	tac	att	cta	att.	ааσ	αta	cta	aaa	aaa	atc	624

Val	Gly	Leu 195	Ile	Gly	Thr	Cys	Ile 200	Leu	Val	Lys	Val	Leu 205	Lys	Lys	Ile	
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											gtt Val					720
											caa Gln					768
											acg Thr					816
											cgc Arg					864
											cta Leu 300					912
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											cag Gln					1008
_	_			_	_	_		_	_	_	tcc Ser		_		_	1056
											ctg Leu					1104
_	-	_	-						_		aac Asn 380		_	-		1152
											gtt Val					1200
											ggc Gly					1248
											agt Ser					1296
											gaa Glu					1344

435 440 445 gca tta ggg ccg gaa ccc gga ggc gaa att agc gta aca ttg cac tac Ala Leu Gly Pro Glu Pro Gly Gly Glu Ile Ser Val Thr Leu His Tyr 450 455 cgt cac ggc tgg ctg cac tgt gaa gtt aat gat gga ccg ggg atc 1440 Arg His Gly Trp Leu His Cys Glu Val Asn Asp Asp Gly Pro Gly Ile 465 470 gea eee gat aaa ate gat eac att ttt gac aaa ggt gte teg aca aaa 1488 Ala Pro Asp Lys Ile Asp His Ile Phe Asp Lys Gly Val Ser Thr Lys 485 490 gga agc gag cga ggc gtc ggt tta gca ctt gtc aaa caa cag gta gaa Gly Ser Glu Arg Gly Val Gly Leu Ala Leu Val Lys Gln Gln Val Glu 505 aat ctc ggc ggc agc atc gcc gtg gaa tcg gaa ccc ggg att ttc aca 1584 Asn Leu Gly Gly Ser Ile Ala Val Glu Ser Glu Pro Gly Ile Phe Thr 520 525 caa ttt ttt gtc cag ata ccc tgg gac ggg gag agg tcg aac aga tga 1632 Gln Phe Phe Val Gln Ile Pro Trp Asp Gly Glu Arg Ser Asn Arg * 535 <210> 247 <211> 987 <212> DNA <213> Escherichia coli <220> <221> CDS <222> (1) ... (987) <400> 247 ttg agt gta ccg ctg tcg aca tgg aat ctt ctg cga tac aac aat tcg Met Ser Val Pro Leu Ser Thr Trp Asn Leu Leu Arg Tyr Asn Asn Ser 10 tat cta cag aag gta act atg ttt cca caa tgc aaa ttt tcc cgc gag Tyr Leu Gln Lys Val Thr Met Phe Pro Gln Cys Lys Phe Ser Arg Glu ttt cta cat cct cgc tac tgg ctc aca tgg ttt ggg ctt ggt gta ctc 144 Phe Leu His Pro Arg Tyr Trp Leu Thr Trp Phe Gly Leu Gly Val Leu tgg ctt tgg gta cag ctt cct tat cct gtt ctc tgc ttt ctc ggc acg 192 Trp Leu Trp Val Gln Leu Pro Tyr Pro Val Leu Cys Phe Leu Gly Thr 55 egt att gge gea atg geg ega eea tte etg aaa egt egt gaa tet ate 240 Arg Ile Gly Ala Met Ala Arg Pro Phe Leu Lys Arg Arg Glu Ser Ile 65

gcc cgt aaa aac ctg gaa ctt tgt ttc ccg cag cat tct gcg gaa gaa' Ala Arg Lys Asn Leu Glu Leu Cys Phe Pro Gln His Ser Ala Glu Glu

85 .

	gag Glu															336
	gaa Glu															384
	ttt Phe 130															432
aat Asn 145	cgc Arg	ggc Gly	gta Val	atg Met	gtt Val 150	gtc Val	ggc	gtc Val	cat His	ttt Phe 155	atg Met	tcg Ser	ctg Leu	gaa Glu	ctg Leu 160	480
	ggc Gly															528
	cat His															576
	tct Ser															624
	gca Ala 210															672
	ggt Gly															720
gtc Val	gcc Ala	aca Thr	acc Thr	aat Asn 245	ggc Gly	acc Thr	tat Tyr	gtt Val	ctc Leu 250	tcc Ser	cgt Arg	ctc Leu	tct Ser	ggc Gly 255	gca Ala	768
_	atg Met	_		_	_	_	-	_			_		_			816
-	ttg Leu						_	_			_		_	_		864
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					gca Ala										96
					gct Ala										144
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					gtc Val										96
	_			-	aaa Lys					_			_		144
		Ser			aaa Lys		Āsp								192

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			aat Asn 100													336
			gat Asp													384
	_		gtc Val						_			_		_		432
			gat Asp					_	_							480
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			aaa Lys													624
	_	_	ata Ile		_		_						_		_	672
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			ctt Leu	_						_	_		_	_		768
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_		-	gtc Val		_			_			_					912

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atg gtt ata tg Met Val Ile Cy	t acc gac s Thr Asp 325	tct aat Ser Asi	Met A	gct aat Ala Asn 330	gtt aat Val Aßr	ttt Phe	aat Asn 335	aat Asn	1008
gcc aat tta ag Ala Asn Leu Se 34	r Asn Cys	cat tto	aac te Asn C	tgt tct Cys Ser	gtt tta Val Leu	aca Thr 350	aaa Lys	gcc Ala	1056
tgg atg ttt aa Trp Met Phe As 355			Arg V			Glu			1104
gtc cag gga at Val Gln Gly Me 370	g ggt att t Gly Ile	acc att Thr Ile 375	ctc c	cgt ggt Arg Gly	gag gaa Glu Glu 380	aat Asn	atc Ile	tcc Ser	1152
att aat agt ga Ile Asn Ser As 385	t atc ctg p Ile Leu 390	Val Th	cta o Leu G	cag aaa Gln Lys 395	ttc ttt Phe Phe	gaa Glu	gaa Glu	gat Asp 400	1200
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Asn 65	Asp	Glu	Leu	Leu	Pro 70	Val	Ala	Arg	Ala	Phe 75	Ser	Gln	Phe	Leu	Asn 80	
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_	_			_	_	gtg Val		_	_		_	_		_		336
	_	_	-	_	_	gaa Glu	_					_		_	_	384
						ctc Leu 135										432
						atg Met									cag Gln 160	480
	_			_		gct Ala	_		_			_	_	_	_	528
_	-	_	-	_		gcc Ala	_					_	-		_	576
						gta Val										624
						caa Gln 215										672
						aac Asn										720
gtt Val	ccg Pro	gtc Val	cgt Arg	ttt Phe 245	act Thr	tcg Ser	tgg Trp	atg Met	ggc Gly 250	ggc Gly	gac Asp	cgc Arg	gac Asp	ggc Gly 255	aac Asn	768
-		_		_	_	atc Ile		_		_	_			_	-	816
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	_	_	_	_	_	gcg Ala 295			_	_	_		_	_		912

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			ggt Gly 580													1776
			ctg Leu	_			_			_	_				_	1824
			gaa Glu													1872
_			gtc Val	_	_	_	_							-	_	1920
			ctg Leu													1968
			ctg Leu 660													2016
			aaa Lys													2064
			ggc													2112
			ggc Gly													2160
			aac Asn		Leu			Pro		Trp						2208
			aaa Lys 740													2256
			gat Asp													2304
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			gac Asp													2400

	gac atc Asp Ile 805	aaa gtg ( Lys Val V	gtg ctg Val Leu 810	gcg att Ala Ile	gcc aac Ala Asn	gat Asp 815	tcc Ser	2448
cat ctg atg gcc His Leu Met Ala 820	Asp Leu	Pro Trp				Leu		2496
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ggt ccg ctg t Gly Pro Leu I 370						
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120 125 115 gte aag gaa gat ate gae gea gag eag ttg get ace gga gae tta teg Val Lys Glu Asp Ile Asp Ala Glu Gln Leu Ala Thr Gly Asp Leu Ser 135 459 gag cga ctg cag gac ttg tct cta taa Glu Arg Leu Gln Asp Leu Ser Leu * <210> 253 <211> 942 <212> DNA <213> Escherichia coli <220> <221> CDS <222> (1)...(942) <400> 253 atg atg gaa aac tat aaa cat act acg gtg ctg ctg gat gaa gcc gtt Met Met Glu Asn Tyr Lys His Thr Thr Val Leu Leu Asp Glu Ala Val 10 aat ggc ctc aat atc cgt cct gat ggc atc tac att gat ggg act ttt Asn Gly Leu Asn Ile Arg Pro Asp Gly Ile Tyr Ile Asp Gly Thr Phe 25 ggt cgc ggt ggt cac tca cgt ctg atc ctc tcg cag ctt ggc gaa gag 144 Gly Arg Gly Gly His Ser Arg Leu Ile Leu Ser Gln Leu Gly Glu Glu 40 ggg cgt ttg ctg gcg atc gat cgc gac ccg cag gct atc gcc gtt gcg 192 Gly Arg Leu Leu Ala Ile Asp Arg Asp Pro Gln Ala Ile Ala Val Ala aag act att gat gat eeg ege tte tee ate ate eae gga eet tte tee 240 Lys Thr Ile Asp Asp Pro Arg Phe Ser Ile Ile His Gly Pro Phe Ser geg etg ggc gaa tac gtt gcc gag egc gat ett atc ggc aag atc gac Ala Leu Gly Glu Tyr Val Ala Glu Arg Asp Leu Ile Gly Lys Ile Asp gge att etc etc gat ett gge gte tet tea eeg eaa ett gat gat get Gly Ile Leu Leu Asp Leu Gly Val Ser Ser Pro Gln Leu Asp Asp Ala gaa egt ggc ttt tee ttt atg ege gat ggt eeg etg gae atg egt atg 384 Glu Arg Gly Phe Ser Phe Met Arg Asp Gly Pro Leu Asp Met Arg Met 120 gae eea ace eqt ggg eag tea gee get gaa tgg eta eaa ace gea gaa Asp Pro Thr Arg Gly Gln Ser Ala Ala Glu Trp Leu Gln Thr Ala Glu 135 gaa gcc qat atc gcc tgg gta ttg aaa acc tat ggt gaa gag cgt ttt Glu Ala Asp Ile Ala Trp Val Leu Lys Thr Tyr Gly Glu Glu Arg Phe 150 155

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ttg cga ttt g Leu Arg Phe 0						144

35 40 45 acg gcg gtg act gtg gta acc acg gcg cac cat acc cgt tta ctg acc 192 Thr Ala Val Thr Val Val Thr Thr Ala His His Thr Arg Leu Leu Thr 55 get cag ege gaa caa etg gtg etg gag ega gat get tta gac att gaa 240 Ala Gln Arg Glu Gln Leu Val Leu Glu Arg Asp Ala Leu Asp Ile Glu 70 tgg cgc aac ctg atc ctt gaa gag aat gcg ctc ggc gac cat agc cgg 288 Trp Arg Asn Leu Ile Leu Glu Glu Asn Ala Leu Gly Asp His Ser Arg gtg gaa agg atc gcc acg gaa aag ctg caa atg cag cat gtt gat ccg 336 Val Glu Arg Ile Ala Thr Glu Lys Leu Gln Met Gln His Val Asp Pro 100 105 tca caa gaa aat atc gta gtg caa aaa taa 366 Ser Gln Glu Asn Ile Val Val Gln Lys * 115 120 <210> 255 <211> 1767 <212> DNA <213> Escherichia coli. <220> <221> CDS <222> (1)...(1767) atg aaa gca gcg gcg aaa acg cag aaa cca aaa cgt cag gaa gaa cat 48 Met Lys Ala Ala Lys Thr Gln Lys Pro Lys Arg Gln Glu Glu His gcc aac ttt atc agt tgg cgt ttt gcg ttg tta tgc ggc tgt att ctc Ala Asn Phe Ile Ser Trp Arg Phe Ala Leu Leu Cys Gly Cys Ile Leu ctg gcg ctg gct ttt ctg ctc gga cgc gta gcg tgg tta caa gtt atc Leu Ala Leu Ala Phe Leu Leu Gly Arq Val Ala Trp Leu Gln Val Ile 40 tee eeg gat atg etg gtg aaa gag gge gae atg egt tet ett ege gtt 192 Ser Pro Asp Met Leu Val Lys Glu Gly Asp Met Arg Ser Leu Arg Val cag caa gtt tee ace tee ege gge atg att act gac egt tet ggt ege Gln Gln Val Ser Thr Ser Arg Gly Met Ile Thr Asp Arg Ser Gly Arg ceg tta geg gtg age gtg ceg gta aaa geg att tgg get gae eeg aaa 288 Pro Leu Ala Val Ser Val Pro Val Lys Ala Ile Trp Ala Asp Pro Lys gaa gtg cat gac gct ggc ggt atc aqc gtc ggt gac cgc tgg aag gcg Glu Val His Asp Ala Gly Gly Ile Ser Val Gly Asp Arg Trp Lys Ala

110

					aat Asn											384
					era aaa											432
					tac Tyr 150											480
_	_	-			cgc Arg	_			_			_			_	528
					act Thr											576
					aaa Lys											624
					tat Tyr											672
_	_	_	_		cac His 230		_		_	_		_	_	_	_	720
-		_	-		cgc Arg	_						_			_	768
					gcc Ala									Glu		816
					agc Ser	Pro		Tyr								864
_	_				atg Met	_		_				_			_	912
					aaa Lys 310											960
					aac Asn											1008
					aaa Lys											1056
acc	999	gta.	tta	cag	aag	tcg	agt	aac	gtc	ggt	gtt	tcc	aag	ctg	gcg	1104

Thr	Gly	Val 355	Leu	Gln	Lys	Ser	Ser 360	Asn	Val	Gly	Val	Ser 365	Lys	Leu	Ala	
	gcg Ala 370															1152
	gga Gly															1200
	cct Pro															1248
	ggc Gly															1296
	act Thr															1344
	gac Asp 450															1392
	act Thr															1440
	gtg Val															1488
	gcg Ala															1536
	tat Tyr															1584
_	gtt Val 530	_			_	_	_									1632
	tcc Ser															1680
	aac Asn															1728
	att Ile											taa *			•	1767

<210> 256

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				gat Asp												672
aaa Lys 225	tgg Trp	ctg Leu	ctt Leu	tat Tyr	tct Ser 230	gag Glu	cat His	cat His	tgc Cys	ggt Gly 235	cag Gln	gcg Ala	att Ile	att Ile	aac Asn 240	720
gcc Ala	gac Asp	gat Asp	gaa Glu	gtg Val 245	ggc Gly	cgc Arg	cgc Arg	tgg Trp	ctg Leu 250	gca Ala	aaa Lys	ctg Leu	ccg Pro	gac Asp 255	gcg Ala	768
gtt Val	gcg Ala	gta Val	tca Ser 260	atg Met	gaa Glu	gat Asp	cat His	att Ile 265	aat Asn	ccg Pro	aac Asn	tgt Cys	cac His 270	gga Gly	cgc Arg	816
				acc Thr												864
				agt Ser												912
				gtc Val												960
				cca Pro 325												1008
				gga Gly												1056
				gat Asp												1104
				cgt Arg												1152
				gat Asp												1200
				ttt Phe 405												1248
_		_	_	ccg Pro	_	_				_		_			_	1296
	_	_		cat His				_	-		_	-	_			1344
act	tgc	gcc	gtt	atg	cag	gct	aaa	gag	aat	gat	gtg	gtà	ctg	gtc	gcg	1392

Thr Cys Ala Val Met Gln Ala Lys Glu Asn Asp Val Val Leu Val Ala ggc aaa ggc cat gaa gat tac cag att gtt ggc aat cag cgt ctg gac 1440 Gly Lys Gly His Glu Asp Tyr Gln Ile Val Gly Asn Gln Arg Leu Asp tac tee gat ege gte acg gtg geg egt etg etg ggg gtg att gea tga 1488 Tyr Ser Asp Arg Val Thr Val Ala Arg Leu Leu Gly Val Ile Ala * 490 . <210> 257 <211> 1359 <212> DNA <213> Escherichia coli <220> <221> CDS <222> (1) ... (1359) <400'> 257 atg att age gta acc ctt age caa ctt acc gac att ctc aac ggt gaa Met Ile Ser Val Thr Leu Ser Gln Leu Thr Asp Ile Leu Asn Gly Glu 10 ctg caa ggt gca gat atc acc ctt gat gct gta acc act gat acc cga Leu Gln Gly Ala Asp Ile Thr Leu Asp Ala Val Thr Thr Asp Thr Arg aaa ctg acg ccg ggc tgc ctg ttt gtt gcc ctg aaa ggc gaa cgt ttt 144 Lys Leu Thr Pro Gly Cys Leu Phe Val Ala Leu Lys Gly Glu Arg Phe gat gcc cac gat ttt gcc gac cag gcg aaa gct ggc ggc gca ggc gca 192 Asp Ala His Asp Phe Ala Asp Gln Ala Lys Ala Gly Gly Ala Gly Ala cta ctg gtt age cgt ccg ctg gac atc gac ctg ccg cag tta atc gtc Leu Leu Val Ser Arg Pro Leu Asp Ile Asp Leu Pro Gln Leu Ile Val aag gat acg cgt ctg gcg ttt ggt gaa ctg gct gca tgg gtt cgc cag 288 Lys Asp Thr Arg Leu Ala Phe Gly Glu Leu Ala Ala Trp Val Arg Gln caa gtt ccg gcg cgc gtg gtt gct ctg acg ggg tcc tcc ggc aaa acc 336 Gin Val Pro Ala Arg Val Val Ala Leu Thr Gly Ser Ser Gly Lys Thr tcc gtt aaa gag atg acg gcg gcg att tta agc cag tgc ggc aac acg 384 Ser Val Lys Glu Met Thr Ala Ala Ile Leu Ser Gln Cys Gly Asn Thr 115 120 ctt tat acg gca ggc aat ctc aac aac gac atc ggt gta ccg atg acg 432 Leu Tyr Thr Ala Gly Asn Leu Asn Asn Asp Ile Gly Val Pro Met Thr 130 ctg ttg cgc tta acg ccg gaa tac gat tac gca gtt att gaa ctt ggc Leu Leu Arg Leu Thr Pro Glu Tyr Asp Tyr Ala Val Ile Glu Leu Gly

145	150	155	160
gcg aac cat cag ggc Ala Asn His Gln Gly 165	gaa ata gcc tgg Glu Ile Ala Trp	act gtg agt ctg act of Thr Val Ser Leu Thr 1 170	ege eeg 528 Arg Pro 175
		gcg gcg cat ctg gaa g Ala Ala His Leu Glu ( 190	
		aaa ggt gaa atc ttt a Lys Gly Glu Ile Phe S 205	
		aac gcc gac aac aac g Asn Ala Asp Asn Asn 2 220	
ctg aac tgg cag agc Leu Asn Trp Gln Ser 225	gta att ggc tca Val Ile Gly Ser 230	cgc aaa gtg tgg cgt t Arg Lys Val Trp Arg 1 235	ttc tca 720 Phe Ser 240
	Ser Asp Phe Thr	gcc acc aat atc cat q Ala Thr Asn Ile His v 250	
		acc cca acc ggt agc g Thr Pro Thr Gly Ser v 270	
		aat att gcg aat gcg ( Asn Ile Ala Asn Ala 1 285	
		gca acg ctt gat gct a Ala Thr Leu Asp Ala : 300	
		cca ggc cgt ctg ttc o Pro Gly Arg Leu Phe 1 315	
	Gln Leu Leu Leu	gac gac tcc tac aac g Asp Asp Ser Tyr Asn 330	
		gta ctg gct gaa atg o Val Leu Ala Glu Met : 350	
tac cgc gtg ctg gtg Tyr Arg Val Leu Val 355	gtg ggc gat atg Val Gly Asp Met 360	gcg gaa ctg ggc gct g Ala Glu Leu Gly Ala g 365	gaa agc 1104 Glu Ser
		gcg gca aaa gct gct g Ala Ala Lys Ala Ala ( 380	
		age cat get ate age age Ser His Ala Ile Ser 395	

agc ggc gtt ggc Ser Gly Val Gly		ala Asp L			1248
ctt aaa tta ctg Leu Lys Leu Leu 420					1296
ggt tca cgt agt Gly Ser Arg Ser 435				Leu Gln Glu	1344
aat ggg aca tgt Asn Gly Thr Cys 450	tag *				1359
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<400> 258 atg tta gtt tgg Met Leu Val Trp 1		ı His Leu Va			48
aac gtc ttt tcc Asn Val Phe Ser · 20					96
gcg ctg ttc atc Ala Leu Phe Ile 35				Ala His Leu	144
caa aaa ctt tcc Gln Lys Leu Ser 50		ı Val Val A			192
cac ttc agc aag His Phe Ser Lys 65					240
acg gcg att gtg Thr Ala Ile Val		Leu Leu T			288
tac gtc tgg tgc Tyr Val Trp Cys 100					336
ttt gtt gat gat Phe Val Asp Asp 115				Lys Gly Leu	384
atc gct cgt tgg	aag tat tt	tgg atg to	cg gtc att gcg	ctg ggt gtc	432

Ile	Ala 130	Arg	Trp	Lys	Tyr	Phe 135	Trp	Met	Ser	Val	Ile 140	Ala	Leu	Glγ	Val	
						gcc Ala										480
						gat Asp										528
	_	_	_			gtc Val								_		576
_		_			_	ggc	_	_		_	_		_		_	624
						gtg Val 215										<b>672</b>
						ccg Pro										720
						gtc Val										768
						gtc Val									gcg Ala	816
			_			att Ile		_	-	_		_	_	_		864
	_					ggc Gly 295										912
						ttt Phe										960
_	_	_				cac His		_	_				_	_	_	1008
						tgg Trp										1056
	_	_	_	_	_	gta Val		taa *								1083

<210> 259

<211> 1317 <212> DNA <213> Escherichia coli <220> <221> CDS <222> (1) ... (1317) <400> 259 atg gct gat tat cag ggt aaa aat gtc gtc att atc ggc ctg ggc ctc Met Ala Asp Tyr Gln Gly Lys Asn Val Val Ile Ile Gly Leu Gly Leu ace ggg ctt tee tgc gtg gae ttt tte ete get ege ggt gtg acg eeg 96 Thr Gly Leu Ser Cys Val Asp Phe Phe Leu Ala Arg Gly Val Thr Pro cgc gtt atg gat acg cgt atg aca ccg cct ggc ctg gat aaa tta ccc 144 Arg Val Met Asp Thr Arg Met Thr Pro Pro Gly Leu Asp Lys Leu Pro 40 gaa gcc gta gaa cgc cac acg ggc agt ctg aat gat gaa tgg ctg atg 192 Glu Ala Val Glu Arg His Thr Gly Ser Leu Asn Asp Glu Trp Leu Met 55 60 geg gea gat etg att gte gee agt eee ggt att gea etg geg eat eea 240 Ala Ala Asp Leu Ile Val Ala Ser Pro Gly Ile Ala Leu Ala His Pro tcc tta agc gct gcc gct gat gcc gga atc gaa atc gtt ggc gat atc 288 Ser Leu Ser Ala Ala Ala Asp Ala Gly Ile Glu Ile Val Gly Asp Ile gag ctg ttc tgt cgc gaa gca caa gca ccg att gtg gcg att acc ggt 336 Glu Leu Phe Cys Arg Glu Ala Gln Ala Pro Ile Val Ala Ile Thr Gly 100 tot aac ggc aaa agc acg gtc acc acg cta gtg ggt gaa atg gcg aaa 384 Ser Asn Gly Lys Ser Thr Val Thr Thr Leu Val Gly Glu Met Ala Lys 115 geg geg ggg gtt aac gtt ggt gtg ggt ggc aat att ggc ctg cct geg 432 Ala Ala Gly Val Asn Val Gly Val Gly Gly Asn Ile Gly Leu Pro Ala 130 ttg atg cta ctg gat gat gag tgt gaa ctg tac gtg ctg gaa ctg tcg 480 Leu Met Leu Leu Asp Asp Glu Cys Glu Leu Tyr Val Leu Glu Leu Ser age tte cag etg gaa ace ace tee age tta cag geg gta gea geg ace 52R Ser Phe Gln Leu Glu Thr Thr Ser Ser Leu Gln Ala Val Ala Ala Thr att ctg aac gtg act gaa gat cat atg gat cgc tat ccg ttt ggt tta 576 Ile Leu Asn Val Thr Glu Asp His Met Asp Arg Tyr Pro Phe Gly Leu caa cag tat cgt gca gca aaa ctg cgc att tac gaa aac gcg aaa gtt 624 Gln Gln Tyr Arg Ala Ala Lys Leu Arg Ile Tyr Glu Asn Ala Lys Val 195 200

		gat Asp						672
		agc Ser 230						720
		gaa Glu						768
		atg Met						816
		gcg Ala						864
		tta Leu						912
		cat His 310						960
		agt Ser						1008
		ttg Leu						1056
		cgt Arg		Asn				1104
		ggc Gly						1152
		act Thr 390						1200
		gat Asp						1248
		aac Asn						1296
		ggt Gly				÷		1317

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					ctg Leu											672
			_		att Ile 230			_		_	_			_	_	720
					cgt Arg											768
			_		tat Tyr	_		_		_						816
_		_			Gly 333						_	_			_	864
					gcg Ala											912
					gtc Val 310											960
					gcg Ala											1008
					ggt Gly											1056
					gtt Val											1104
Thr		Gly	Leu	Thr	ttg Leu	Pro	Leu	Ile	Ser	Tyr		Gly				1152
					gcc Ala 390											1200
acg Thr	cgt Arg	ctg Leu	gag Glu	aaa Lys 405	gcg Ala	cag Gln	gcg Ala	ttt Phe	gta Val 410	cga Arg	ggt Gly	tca Ser	cga Arg	tga *		1245

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<211> 1068

<212> DNA

<213> Escherichia coli

<220>

<221> CDS <222> (1) ... (1068)

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1 5 10

gga cat gta ttc ccg gga ctg gcg gtt gcg cac cat cta atg gct cag 96 Gly His Val Phe Pro Gly Leu Ala Val Ala His His Leu Met Ala Gln 20 25 30

ggt tgg caa gtt cgc tgg ctg ggg act gcc gac cgt atg gaa gcg gac 144 Gly Trp Gln Val Arg Trp Leu Gly Thr Ala Asp Arg Met Glu Ala Asp 35 40 45

tta gtg cca aaa cat ggc atc gaa att gat ttc att cgt atc tct ggt 192 Leu Val Pro Lys His Gly Ile Glu Ile Asp Phe Ile Arg Ile Ser Gly 50 55 60

ctg cgt gga aaa ggt ata aaa gca ctg ata gct gcc ccg ctg cgt atc 240 Leu Arg Gly Lys Gly Ile Lys Ala Leu Ile Ala Ala Pro Leu Arg Ile 65 70 75 80

ttc aac gcc tgg cgt cag gcg cgg gcg att atg aaa gcg tac aaa cct 288
Phe Asn Ala Trp Arg Gln Ala Arg Ala Ile Met Lys Ala Tyr Lys Pro
85 90 95

gac gtg gtg ctc ggt atg gga ggc tac gtg tca ggt cca ggt ggt ctg 336 Asp Val Val Leu Gly Met Gly Gly Tyr Val Ser Gly Pro Gly Gly Leu 100 105 110

gcc gcg tgg tcg tta ggc att ccg gtt gta ctt cat gaa caa aac ggt 384
Ala Ala Trp Ser Leu Gly Ile Pro Val Val Leu His Glu Gln Asn Gly
115 120 125

att gcg ggc tta acc aat aaa tgg ctg gcg aag att gcc acc aaa gtg 432 Ile Ala Gly Leu Thr Asn Lys Trp Leu Ala Lys Ile Ala Thr Lys Val 130 135 140

atg cag gcg ttt cca ggt gct ttc cct aat gcg gaa gta gtg ggt aac 480 Met Gln Ala Phe Pro Gly Ala Phe Pro Asn Ala Glu Val Val Gly Asn 145 150 155

ccg gtg cgt acc gat gtg ttg gcg ctg ccg ttg ccg cag caa cgt ttg 528 Pro Val Arg Thr Asp Val Leu Ala Leu Pro Leu Pro Gln Gln Arg Leu 165 170 175

gct gga cgt gaa ggt ccg gtt cgt gtg ctg gta gtg ggt ggt tct cag 576 Ala Gly Arg Glu Gly Pro Val Arg Val Leu Val Val Gly Gly Ser Gln 180 185 190

ggc gca cgc att ctt aac cag aca atg ccg cag gtt gct gcg aaa ctg 624 Gly Ala Arg Ile Leu Asn Gln Thr Met Pro Gln Val Ala Ala Lys Leu 195 200 205

ggt gat tca gtc act atc tgg cat cag agc ggc aaa ggt tcg caa caa 672 Gly Asp Ser Val Thr Ile Trp His Gln Ser Gly Lys Gly Ser Gln Gln 210 215 220

tee gtt gaa cag geg tat gee gaa geg ggg caa eeg cag cat aaa gtg 720

225	Gln Ala	Tyr A 230	la Glu	Ala	Gly	Gln 235	Pro	Gln	His	Lys	Val 240	
acg gaa ttt Thr Glu Phe				Ala .								768
gtc gtt tgc Val Val Cys	cgc tcc Arg Ser 260	ggt g Gly A	cg tta la Leu	acg Thr 265	gtg Val	agt Ser	gaa Glu	atc Ile	gcc Ala 270	gcg Ala	gca Ala	816
gga cta ccg Gly Leu Pro 275	gcg ttg Ala Leu	ttt g Phe V	tg ccg al Pro 280	ttt Phe	caa Gln	cat His	aaa Lys	gac Asp 285	cgc Arg	cag Gln	caa Gln	864
tac tgg aat Tyr Trp Asn 290	gcg cta Ala Leu	Pro L	tg gaa eu Glu 95	aaa Lys	gcg Ala	gly ggc	gca Ala 300	gcc Ala	aaa Lys	att Ile	atc Ile	912
gag cag cca Glu Gln Pro 305			al Asp									960
tgg tcg cga Trp Ser Arg	gaa acc Glu Thr 325	tta t Leu L	ta acc eu Thr	Met	gca Ala 330	gaa Glu	cgc Arg	gcc Ala	ege Arg	gct Ala 335	gca Ala	1008
tcc att ccg Ser Ile Pro	gat gcc Asp Ala 340	acc g Thr G	ag cga lu Arg	gtg Val 345	gca Ala	aat Asn	gaa Glu	gtg Val	agc Ser 350	cgg Arg	gtt Val	1056
gcc cgg gcg Ala Arg Ala 355	taa *											1068
Ala Arg Ala	*	oli										1068
Ala Arg Ala 355 <210> 262 <211> 1476 <212> DNA	* richia c	oli										1068
Ala Arg Ala 355 <210> 262 <211> 1476 <212> DNA <213> Esche: <220> <221> CDS	* richia c . (1476) caa caa	ttg g										1068
Ala Arg Ala 355 <210> 262 <211> 1476 <212> DNA <213> Esche: <220> <221> CDS <222> (1) <400> 262 atg aat aca Met Asn Thr	* richia c .(1476)  caa caa Gln Gln 5  cgg cac	ttg g Leu A	la Lys	Leu	Arg 10 ggc	Ser	Ile ggt	Val ggt	Pro	Glu 15 ggt	Met atg	
Ala Arg Ala 355  <210> 262 <211> 1476 <212> DNA <213> Esche: <220> <221> CDS <222> (1) <400> 262 atg aat aca Met Asn Thr 1  cgt cgc gtt	* richia c .(1476)  caa caa Gln Gln 5  cgg cac Arg His 20  gcc gaa	ttg g Leu A ata c Ile H	la Lys at ttt is Phe	gtc Val 25	Arg 10 ggc Gly gaa	Ser att Ile	ggt Gly	yal ggt Gly	gcc Ala 30	Glu 15 ggt Gly agt	Met atg Met	48

		att Ile														.240
gtg Val	gtc Val	gtt Val	gtt Val	tcc Ser 85	agc Ser	gcg Ala	att Ile	tct Ser	gcc Ala 90	gat Asp	aac Asn	ccg Pro	gaa Glu	att Ile 95	gtc Val	288
		cat His														336
		tta Leu 115														384
		acg Thr														432
999 Gly 145	ctc Leu	gac Asp	cca Pro	acc Thr	ttc Phe 150	gtt Val	aac Asn	ggc Gly	Gly	ctg Leu 155	gta Val	aaa Lys	gcg Ala	gcg Ala	160 Gly 999	480
		gcg Ala														528
gag Glu	agt Ser	gat Asp	gca Ala 180	tcg Ser	ttc Phe	ctg Leu	cat His	ctg Leu 185	caa Gln	ccg Pro	atg Met	gtg Val	gcg Ala 190	att Ile	gtc Val	576
acc Thr	aat Asn	atc Ile 195	gaa Glu	gcc Ala	gac Asp	cac His	atg Met 200	gat Asp	acc Thr	tac Tyr	cag Gln	ggc Gly 205	gac Asp	ttt Phe	gag Glu	624
		aaa Lys														672
		gcg Ala		Met												720
		gtg Val														768
gac Asp	gtg Val	cgt Arg	gta Val 260	gaa Glu	gat Asp	tat Tyr	cag Gln	cag Gln 265	att Ile	ggc	ccg Pro	Gl¤ Cag	999 Gly 270	cac His	ttt Phe	816
acg Thr	ctg Leu	ctg Leu 275	cgc Arg	cag Gln	gac Asp	aaa Lys	gag Glu 280	ccg Pro	atg Met	ege Arg	gtc Val ;	acc Thr 285	ctg Leu	aat Asn	gcg Ala	864
cca Pro	ggt Gly 290	cgt Arg	cat His	aac Asn	gcg Ala	ctg Leu 295	aac Asn	gcc Ala	gca Ala	gct Ala	gcg Ala 300	gtt Val	gcg Ala	gtt Val	gct Ala	912

acg g Thr G																960
ttc o	cag 31n	gly aaa	act Thr	ggt Gly 325	cgc Arg	cgt Arg	ttt Phe	gat Asp	ttc Phe 330	ctc Leu	ggt Gly	gaa Glu	Phe	ccg Pro 335	ctg Leu	1008
gag d Glu I																1056
ggc o																1104
ggc t Gly 1	tgg Frp 370	ccg Pro	gat Asp	aaa Lys	aac Asn	ctg Leu 375	gta Val	atg Met	ctg Leu	ttt Phe	cag Gln 380	ccg Pro	cac His	cgt Arg	ttt Phe	1152
acc o Thr A 385	egt Arg	acg Thr	cgc Arg	gac Asp	ctg Leu 390	tat Tyr	gat Asp	gat Asp	ttc Phe	gcc Ala 395	aat Asn	gtg Val	ctg Leu	acg Thr	cag Gln 400	1200
gtt g Val A																1248
att o																1296
Gly I																1344
atg o																1392
gct g Ala 0 465																1440
aag ( Lys l																1476
<210: <211: <212: <213:	> 92 > Dì	21 VA	rich:	ia co	oli								ı			».
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1				5					10				15		
					tct Ser										96
					tat Tyr										144
					ggc Gly										192
					ggt Gly 70										240
					agc Ser										288
					ctt Leu										336
					acc Thr										384
					att Ile										432
_	_	_	-		tcc Ser 150	_						 -		_	480
	_			_	gca Ala		_	_	_		_	_	_	_	528
	_			_	tgg Trp		_		_			 ~			576
					tta Leu										624
					gcg Ala										672
					gaa Glu 230										720
					acg Thr					Lys					768

gac gtt atg Asp Val Met	ctg gac a Leu Asp 3 260	agc gat Ser Asp	Gly (	cag Gln: 265	ttt Phe	tat Tyr	ctg Leu	ctg Leu	gaa Glu 270	gcc Ala	aat Asn	816
acc tca ccg Thr Ser Pro 275	ggt atg a Gly Met '	acc agc Thr Ser	cac His 280	agc Ser	ctg Leu	gtg Val	ccg Pro	atg Met 285	geg Ala	gca Ala	egt Arg	864
cag gca ggt Gln Ala Gly 290												912
gcg gac taa Ala Asp * 305												921
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gtg caa caa Val Gln Gln												96
ttt acc ggc Phe Thr Gly 35												144
gag gag gcg Glu Glu Ala 50												192
gac aat gtt Asp Asn Val 65												240
gat cgt aaa Asp Arg Lys												288
gtt gaa gcc Val Glu Ala			Leu									336
gcc gaa cgc Ala Glu Arg 115				Arg								384
gaa gtg ttt	gtc gat	acg ccg	ctg	gcg	att	tgc	gaa	gcc	cgc	gat	ccc	432

Glu	Val 130	Phe	Val	Asp	Thr	Pro 135	Leu	Ala	Ile	Сув	Glu 140	Ala	Arg	Asp	Pro	
	ggc Gly													Phe		480
	ata Ile															528
	ggt Gly															576
_	aga Arg	_		_			_		tga *							606
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	0> 1> C1 2> (:		. (142	28)												
atg	0> 26 aac Asn	acc	_		_				_		_			_	_	48
	tgg Trp															96
	ggt Gly															144
	gat Asp 50															192
gac Asp 65	agt Ser	aag Lys	cgt Arg	cac His	ggc Gly 70	acc Thr	cag Gln	Gly ggc	gaa Glu	aag Lys 75	ctg Leu	gat Asp	ctg Leu	gct Ala	ctg Leu 80	240
	gtg Val															288
	gcc Ala															336
	acc Thr															384

tcg ac Ser Th	r Cys														432
ctc ga Leu As 145	t caa p Gln	acc Thr	cgt Arg	cgt Arg 150	cac His	agt Ser	ttt Phe	atc Ile	tcc Ser 155	aca Thr	ctg Leu	ttg Leu	eja aaa	atc Ile 160	480
aaa ca Lys Hi															528
gaa ga Glu Gl	-			_		_	-	_		-			_		576
cag ct Gln Le															624
gaa gg Glu Gl 21	y Asp	aac Asn	gtg Val	gca Ala	tcg Ser 215	caa Gln	agt Ser	gaa Glu	agt Ser	atg Met 220	ccg Pro	tgg Trp	tac Tyr	agc Ser	672
ggt cc Gly Pr 225															720
gtg ga Val As															768
aat ct Asn Le															816
gaa gt Glu Va															864
gtc gc Val Al 29	a Arg														912
gga ga Gly Gl 305	a gcg u Ala	atc Ile	acc Thr	ctg Leu 310	gtg Val	ctg Leu	acg Thr	gat Asp	gag Glu 315	atc Ile	gac Asp	atc Ile	agc Ser	cgt Arg 320	960
ggc ga Gly As															1008
gcg to Ala Se															1056
cag ag Gln Se		Asp													1104

gat ggc att cgc tai Asp Gly Ile Arg Ty 370				<b>i</b> 2
gtt gaa aac ctg cca Val Glu Asn Leu Pro 385				łO
gac gag ccg ctg gtg Asp Glu Pro Leu Val 409	. Leu Asp Arg			.8
ggg ctg att ttt atc Gly Leu Ile Phe Ile 420	Asp Arg Leu			)6
atg gtg cac gag cca Met Val His Glu Pro 435				.4
agt gca ttc gaa ctg Ser Ala Phe Glu Let 450	-		-	)2
cac tgg ggc gcg cgc His Trp Gly Ala Arc 465			142	:8
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<211> 384 <212> DNA <213> Escherichia ( <220> <221> CDS	ragt ggt cgt			
<pre>&lt;211&gt; 384 &lt;212&gt; DNA &lt;213&gt; Escherichia </pre> <220> <221> CDS <222> (1)(384) <400> 266 atg cgc cat cgt aag Met Arg His Arg Lys	agt ggt cgt s Ser Gly Arg s cgc aat atg s	Gln Leu Asn Arg 10 gca ggt tca ctg	Asn Ser Ser His 15 gtt cgt cat gaa 96	
<pre>&lt;211&gt; 384 &lt;212&gt; DNA &lt;213&gt; Escherichia (  &lt;220&gt; &lt;221&gt; CDS &lt;222&gt; (1)(384)  &lt;400&gt; 266 atg cgc cat cgt aag Met Arg His Arg Lys 1 5  cgc cag gct atg ttc Arg Gln Ala Met Pho</pre>	agt ggt cgt sees sees Gly Arg sees aat atg sees Arg Asn Met sees ctg cct aaa	Gln Leu Asn Arg 10  gca ggt tca ctg Ala Gly Ser Leu 25  gcg aaa gag ctg	Asn Ser Ser His 15 gtt cgt cat gaa 96 Val Arg His Glu 30 cgc cgc gta gtt 144	:
<pre>&lt;211&gt; 384 &lt;212&gt; DNA &lt;213&gt; Escherichia (  &lt;220&gt; &lt;221&gt; CDS &lt;222&gt; (1)(384)  &lt;400&gt; 266 atg cgc cat cgt aag Met Arg His Arg Lys 1 5  cgc cag gct atg ttc Arg Gln Ala Met Phe 20  atc atc aag acg act Ile Ile Lys Thr Th</pre>	agt ggt cgt sees agt ggt sees agt atg sees agt atg sees agt atg sees agt atg sees agt agt sees agt sees agt sees agg see	Gln Leu Asn Arg 10  gca ggt tca ctg Ala Gly Ser Leu 25  gcg aaa gag ctg Ala Lys Glu Leu act gat agc gtt	Asn Ser Ser His  15  gtt cgt cat gaa 96  Val Arg His Glu 30  cgc cgc gta gtt 144  Arg Arg Val Val 45  gct aat cgt cgt 192	
<pre>&lt;211&gt; 384 &lt;212&gt; DNA &lt;213&gt; Escherichia (  &lt;220&gt; &lt;221&gt; CDS &lt;222&gt; (1) (384)  &lt;400&gt; 266 atg cgc cat cgt aag Met Arg His Arg Lys 1 5  cgc cag gct atg ttc Arg Gln Ala Met Phe 20  atc atc aag acg act Ile Ile Lys Thr Thr 35  gag ccg ctg att act Glu Pro Leu Ile Thr</pre>	agt ggt cgt Ser Gly Arg cgc aat atg Arg Asn Met ctg cct aaa Leu Pro Lys 40 ctt gcc aag Leu Ala Lys 55	Gln Leu Asn Arg 10  gca ggt tca ctg Ala Gly Ser Leu 25  gcg aaa gag ctg Ala Lys Glu Leu  act gat agc gtt Thr Asp Ser Val 60  aac gag atc gtg	Asn Ser Ser His  15  gtt cgt cat gaa 96  Val Arg His Glu 30  cgc cgc gta gtt 144  Arg Arg Val Val 45  gct aat cgt cgt 192  Ala Asn Arg Arg  gca aaa ctg ttt 240	•

85 90 95

att ctg aag tgt ggc ttc cgt gca ggc gac aac gcg ccg atg gct tac 336

Ile Leu Lys Cys Gly Phe Arg Ala Gly Asp Asn Ala Pro Met Ala Tyr

100 105 110

atc gag ctg gtt gat cgt tca gag aaa gca gaa gct gct gca gag taa 384 Ile Glu Leu Val Asp Arg Ser Glu Lys Ala Glu Ala Ala Glu * 115 120 125

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<220>

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Met Gln Gly Ser Val Thr Glu Phe Leu Lys Pro Arg Leu Val Asp Ile
1 10 15

gag caa gtg agt tcg acg cac gcc aag gtg acc ctt gag cct tta gag 96 Glu Gln Val Ser Ser Thr His Ala Lys Val Thr Leu Glu Pro Leu Glu 20 25 30

cgt ggc ttt ggc cat act ctg ggt aac gca ctg cgc cgt att ctg ctc 144 Arg Gly Phe Gly His Thr Leu Gly Asn Ala Leu Arg Arg Ile Leu Leu 35 40 45

tca tcg atg ccg ggt tgc gcg gtg acc gag gtt gag att gat ggt gta 192 Ser Ser Met Pro Gly Cys Ala Val Thr Glu Val Glu Ile Asp Gly Val

cta cat gag tac agc acc aaa gaa ggc gtt cag gaa gat atc ctg gaa 240 Leu His Glu Tyr Ser Thr Lys Glu Gly Val Gln Glu Asp Ile Leu Glu 65 70 75 80

atc ctg ctc aac ctg aaa ggg ctg gcg gtg aga gtt cag ggc aaa gat 288

Ile Leu Leu Asn Leu Lys Gly Leu Ala Val Arg Val Gln Gly Lys Asp

85 90 95

gaa gtt att ctt acc ttg aat aaa tct ggc att ggc cct gtg act gca 336 Glu Val Ile Leu Thr Leu Asn Lys Ser Gly Ile Gly Pro Val Thr Ala 100 105 110

gcc gat atc acc cac gac ggt gat gtc gaa atc gtc aag ccg cag cac
Ala Asp Ile Thr His Asp Gly Asp Val Glu Ile Val Lys Pro Gln His
115 120 125

gtg atc tgc cac ctg acc gat gag aac gcg tct att agc atg cgt atc 432
Val Ile Cys His Leu Thr Asp Glu Asn Ala Ser Ile Ser Met Arg Ile
130 135 140

aaa gtt cag cgc ggt cgt ggt tat gtg ccg gct tct acc cga att cat
Lys Val Gln Arg Gly Arg Gly Tyr Val Pro Ala Ser Thr Arg Ile His
145 150 155 160

	gaa Glu															528
	agc Ser															576
	cag Gln															624
	aca Thr 210															672
	gaa Glu															720
_	gtg Val		_						_	_		_	-	_		768
	gac Asp															816
	gct Ala															864
	ctt Leu 290															912
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	cca Pro	-	_	_		-	_		taa *							990
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	)> .> CI !> (1		(623	L}												
atg	)> 26 gca Ala	aga														48
acc	gac	tta	ttc	ctt	aag	tct	ggc	gtt	cgc	gcg	atc	gat	acc	aag	tgt	96

Thr Asp Leu	Phe Leu 20	Lys Ser	Gly	Val 25	Arg	Ala	Ile	Asp	Thr 30	Lys	Cys	
aaa att gaa Lys Ile Glu 35	_		_				_		_	_	-	144
tct gac tat Ser Asp Tyr 50			_	_	_			_	-	-		192
tat ggt gtg Tyr Gly Val 65				_					-	_	_	240
cgt ctg aaa Arg Leu Lys												288
cgt ctg gac Arg Leu Asp	_	_	Arg	_				_		_	_	336
gaa gca cgt Glu Ala Arg 115												384
gtt gtt aac Val Val Asn 130												432
att cgt gag Ile Arg Glu 145		-	_		_			_	_	_		480
ctg gct gag Leu Ala Glu				Thr		_	_	_	-	_		528
aag atg gaa Lys Met Glu		_	Arg :	_	_		_		-	_		576
gcg gac att Ala Asp Ile 195										taa *		621
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Т				5					TO					15		
				gct Ala												96
			_	cgt Arg	_				_			_		_		144
				cgt Arg			_				-		-	_	-	192
_	_	_		cgt Arg	_	-	_	_			_				_	240
	_	_	_	atg Met 85	_			-				_	-			288
				aac Asn												336
		-		cct Pro				_	_	_	_			_		384
gta Val	taa *															390
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				tcg Ser												96
				gcg Ala												144
				atc Ile												192

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_		_	atc Ile		aaa Lys	taa *										357
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	L> CI		. (138	33)											· 8 · .	
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					gtc Val											96
					ttc Phe											144
	_	-		_	gtg Val		_	-	_		_	_	_	_		192
					acc Thr 70											240
ctg Leu	ctg Leu	tgg Trp	Gly ggg	gcc Ala 85	atc Ile	ccg Pro	ttc Phe	ggc Gly	atc Ile 90	gtc Val	tgc Cys	gtg Val	ctg Leu	acc Thr 95	ttc Phe	288
					tcc Ser											336
					acc Thr											384
					gtc Val											432

130 135 140 ctg cag tee tgg ege tte tte etg geg geg geg gge teg ete get ate 480 Leu Gln Ser Trp Arg Phe Phe Leu Ala Ala Ala Gly Ser Leu Ala Ile 145 150 age gge ate geg etg eeg etg gtg age ate ate gge aaa ggg gae gag 528 Ser Gly Ile Ala Leu Pro Leu Val Ser Ile Ile Gly Lys Gly Asp Glu cag gtg ggc tac ttc ggc gcc atg tgc gtg ctg ggg ctg agc ggc gtg 576 Gln Val Gly Tyr Phe Gly Ala Met Cys Val Leu Gly Leu Ser Gly Val gtg ctg ctc tac gtc tgc ttc ttc acg acc aaa gag cgc tac acc ttt 624 Val Leu Leu Tyr Val Cys Phe Phe Thr Thr Lys Glu Arg Tyr Thr Phe gag gtg cag ceg ggc teg teg gtg geg aaa gac ett aag etg etg etg 672 Glu Val Gln Pro Gly Ser Ser Val Ala Lys Asp Leu Lys Leu Leu Leu 210 215 gge aac age cag tgg cgc atc atg tgc gcg ttc aag atg atg gcg acc 720 Gly Asn Ser Gln Trp Arg Ile Met Cys Ala Phe Lys Met Met Ala Thr 225 230 235 tgc tcc aac gtg gtg cgc ggc ggg gcg acg ctc tac ttc gtg aaa tac 768 Cys Ser Asn Val Val Arg Gly Gly Ala Thr Leu Tyr Phe Val Lys Tyr 245 250 gtg atg gat cac ccg gag ttg gcg acc cag ttt tta ctt tac ggc agc 816 Val Met Asp His Pro Glu Leu Ala Thr Gln Phe Leu Leu Tyr Gly Ser 265 260 ctc gcc acc atg ttc ggc tcg ctt tgc tcc tca cgc ctg ctg ggc cgc 864 Leu Ala Thr Met Phe Gly Ser Leu Cys Ser Ser Arg Leu Leu Gly Arg 280 tte gae ege gte ace gee tte aag tgg ate ate gte gee tae teg etg 912 Phe Asp Arg Val Thr Ala Phe Lys Trp Ile Ile Val Ala Tyr Ser Leu atc agc ctg ctg att ttc gtc acc ccg gcg gag cac atc gcg ctc att 960 Ile Ser Leu Leu Ile Phe Val Thr Pro Ala Glu His Ile Ala Leu Ile 305 310 315 ttt gcc ctc aac atc ctg ttc ctg ttc gtc ttt aat acc acc acg ccg 1008 Phe Ala Leu Asn Ile Leu Phe Leu Phe Val Phe Asn Thr Thr Pro 330 325 335 ctg cag tgg ctg atg gct tct gac gtg gtg gac tac gag gag agc cgc 1056 Leu Gln Trp Leu Met Ala Ser Asp Val Val Asp Tyr Glu Glu Ser Arg 340 345 age ggt ege ege ete gae ggg etg gtg tte tee ace tae etg tte age 1104 Ser Gly Arg Arg Leu Asp Gly Leu Val Phe Ser Thr Tyr Leu Phe Ser 360 365 ctg aag att ggc ctg gcg att ggc ggg gcg gtg gtg ggc tgg atc ctg 1152 Leu Lys Ile Gly Leu Ala Ile Gly Gly Ala Val Val Gly Trp Ile Leu

375

380

370

geg tac gtc aac tat tec gcc age age age gtg cag ceg gtt gag gtg Ala Tyr Val Asn Tyr Ser Ala Ser Ser Ser Val Gln Pro Val Glu Val 385 390 395 400	
ctc acc acc atc aaa att ctg ttc tgc gtg gtg ccg gtg gtg ctc tac Leu Thr Thr Ile Lys Ile Leu Phe Cys Val Val Pro Val Val Leu Tyr 405 410 415	
gcg ggc atg ttc atc atg ctg tcg ctc tac aag ctc acc gat gcc cgc Ala Gly Met Phe Ile Met Leu Ser Leu Tyr Lys Leu Thr Asp Ala Arg 420 425 430	
gtg gag gcc atc agc cgg cag ctg att aag cac cgc gcg gcg cag ggc Val Glu Ala Ile Ser Arg Gln Leu Ile Lys His Arg Ala Ala Gln Gly 435 440 445	1344
gag gcc gtt ccc gac gcc gcg aca gcc gca tcc cat taa Glu Ala Val Pro Asp Ala Ala Thr Ala Ala Ser His * 450 455 460	1383
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ctg tgc cgc cag ggc gag gac tac tac atc gcc acc tcg acc ttc gag Leu Cys Arg Gln Gly Glu Asp Tyr Tyr Ile Ala Thr Ser Thr Phe Glu 20 25 30	
tgg ttc ccg ggc gtg cgc atc tac cac tcc cgt gac ctg aaa aac tgg Trp Phe Pro Gly Val Arg Ile Tyr His Ser Arg Asp Leu Lys Asn Trp 35 40 45	
tcg ctg gtc agc acc ccg ttg gac cgc gtg tcg atg ctg gac atg aag Ser Leu Val Ser Thr Pro Leu Asp Arg Val Ser Met Leu Asp Met Lys 50 55 60	
ggc aac ccg gac tcc ggc ggc atc tgg gcg ccg tgc ctg agc tac gcc Gly Asn Pro Asp Ser Gly Gly Ile Trp Ala Pro Cys Leu Ser Tyr Ala 65 70 75 80	L
gac ggt aaa ttc tgg ctg ctc tac acc gac gtg aag att gtc gac tcg Asp Gly Lys Phe Trp Leu Leu Tyr Thr Asp Val Lys Ile Val Asp Ser 85 90 95	
ccg tgg aaa aac ggc cgc aac ttc ctc gtc acc gcg ccc tcc atc gag Pro Trp Lys Asn Gly Arg Asn Phe Leu Val Thr Ala Pro Ser Ile Glu 100 105 110	
ggg cca tgg agc gag cca atc ccg atg ggc aac ggc ggg ttt gac ccg	384

Gly	Pro	Trp 115	Ser	Glu	Pro	Ile	Pro 120	Met	Gly	Asn	Gly	Gly 125	Phe	Asp	Pro	
	ctg Leu 130															432
	glå aaa	-	_			_		_							cag Gln : 160	480
	ttt Phe														ctg . Leu	528
	acc Thr		_	_		-			_				_		_	576
	gcg Ala															624
	cac His 210															672
	ctg Leu															720
	ccg Pro															768
	gaa Glu			-	_				_	_	_	_	_	_		816
	gtg Val	_	_	_	_				_			_	_	_		864
	gag Glu 290															912
	gaa Glu															960
	gag Glu															1008
	agt Ser															1056
gac Asp	acc Thr	ctc Leu	ggc Gly	tcg Ser	Leu	acc Thr	gcg Ala	cgc Arg	ccg Pro	gly ggc	ttc Phe	tta Leu	cgg Arg	ctc Leu	tat Tyr	1104

360 365 355 qqc aac qac teq etc aat teg ace ttc ace caa teg ace gtg geg ege 1152 Gly Asn Asp Ser Leu Asn Ser Thr Phe Thr Gln Ser Thr Val Ala Arg 375 380 ege tgg cag cac ttc gcc ttc egg gca gaa acg egg atg gag ttc teg 1200 Arg Trp Gln His Phe Ala Phe Arg Ala Glu Thr Arg Met Glu Phe Ser 390 395 ceg gtg cac ttc cag cag age geg ggg ctg ace tgc tac tac aac age 1248 Pro Val His Phe Gln Gln Ser Ala Gly Leu Thr Cys Tyr Tyr Asn Ser 405 410 aaa aac tgg agc tac tgc ttt gtg gac tac gag gag gga cag ggt aga 1296 Lys Asn Trp Ser Tyr Cys Phe Val Asp Tyr Glu Glu Gly Gln Gly Arg 420 425 acc atc aaa gtt atc cag ctc gac cac aac gtg ccg tcg tgg ccg ctg 1344 Thr Ile Lys Val Ile Gln Leu Asp His Asn Val Pro Ser Trp Pro Leu 440 435 cac gag cag ccc att ccg gtg ccg gaa cat gcg gag agc gtc tgg ctg. 1392 His Glu Gln Pro Ile Pro Val Pro Glu His Ala Glu Ser Val Trp Leu 450 455 cgg gtg gac gtg gat acg ctg gtc tac cgc tac agc tac tcg ttt gat 1440 Arg Val Asp Val Asp Thr Leu Val Tyr Arg Tyr Ser Tyr Ser Phe Asp 465 470 ggc gag acg tgg cac acc gtg ccg gtg acg tat gag gcg tgg aag ctg Gly Glu Thr Trp His Thr Val Pro Val Thr Tyr Glu Ala Trp Lys Leu 485 teq gae gae tae ate gge ggg ege gge tte tte ace gge geg ttt gtg 1536 Ser Asp Asp Tyr Ile Gly Gly Arg Gly Phe Phe Thr Gly Ala Phe Val 500 505 gge etg cae tge gag gae ate age gge gae gge tge tae geg gae tte 1584 Gly Leu His Cys Glu Asp Ile Ser Gly Asp Gly Cys Tyr Ala Asp Phe 520 . 525 gac tac ttc acc tac gag ccg gtc taa 1611 Asp Tyr Phe Thr Tyr Glu Pro Val * 530 535 <210> 273 <211> 978 <212> DNA <213> Escherichia coli <220> <221> CDS <222> (1)...(978) <400> 273 ttg cat atg aaa aaa ata atc ttt gct ttt att ata tta ttt gtg ttt Met His Met Lys Lys Ile Ile Phe Ala Phe Ile Ile Leu Phe Val Phe

10

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		ccc Pro 35														144
		aca Thr														192
_		agg Arg		_	-					_		_	_	_		240
_	_	gtt Val		_	_	_	_			_						288
		gtt Val														336
	_	cat His 115		-		-	_	_		-		_		-		384
		ccg Pro													ctc Leu ,	432
_	_	gca Ala	_	_			_		_	_				-	_	480
		gcc Ala														528
		agc Ser					Ala		Leu							576
		gca Ala 195														624
_		tac Tyr			_	_	_						_			672
_		att Ile	_		_		_		_	_			_	_	_	720
		aaa Lys														768
atg	aat	acc	cca _.	ggg	ttt	att	ccc	ggt	att	gat	ttc	tct	gac	cac	ctg	816

Met Asn Thr	Pro Gly 260	Phe Il	e Pro	Gly 265	Ile	Asp	Phe	Ser	Asp 270	His	Leu	
aat tat tgg Asn Tyr Trp 275												864
ttt tat egt Phe Tyr Arg 290			r His									912
ttg aat tat Leu Asn Tyr 305	_											960
tta tac aac Leu Tyr Asn	•	taa *			•							978
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gta eeg ege Val Pro Arg			_	_		_	-					288
cca gat gcg Pro Asp Ala												336
	100 Alg	014 01		105					110			

	att Ile 130															432
	gtt Val															480
	cgc Arg															528
	gct Ala															576
	tat Tyr															624
Ile	ggc Gly 210	Met	Arg	Val	Ser	Ser 215	Gly	Cys	Ile	Arg	Leu 220	Arg	Asp	Āsp	Asp	672
Ile 225		Thr	Leu	Phe	Ser 230	Gln	Val	Thr	Pro	Gly 235	Thr	Lys	Val	Asn	Ile 240	720
Ile	aac Asn	Thr	Pro	Ile 245	Lys	Val	Ser	Ala	Glu 250	Pro	Asn	Gly	Ala	Arg 255	Leu	768
Val	gaa Glu	Val	His 260	Gln	Pro	Leu	Ser	Glu 265	Lys	Ile	Āsp	Asp	Asp 270	Pro	Gln	816
Leu	ctg Leu	Pro 275	Ile	Thr	Leu	Asn	Ser 280	Ala	Met	Gln	Ser	Phe 285	Lys	Asp	Ala	864
Ala	caa Gln 290	Thr	Āsp	Āla	Glu	Val 295	Met	Gln	His	Val	Met 300	Āsp	Val	Arg	Ser	912
Gly 305																960
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<211> 1485

<212> DNA

<213> Escherichia coli

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225	230	235	240
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Thr Ala Leu	•	 caa tog otg acg Gln Ser Leu Th	-
		ggt att ttc ttt Gly Ile Phe Phe 28	e Ile Arg Arg
		ccg gtg gat tta Pro Val Asp Let 300	
		tct gtt tgc tct Ser Val Cys Ser 315	
		ttt tac ctg cas Phe Tyr Leu Gli 330	
Gly Arg Ser		ctt ctg aca ccg Leu Leu Thr Pro	
		ggc tat ttg att Gly Tyr Leu Ile 369	e Glu Arg Val
		ttg ttc atc atc Leu Phe Ile Met 380	
		tca cct gcg gat Ser Pro Ala Asp 395	
		gga ttt ggc tta Gly Phe Gly Let 410	
Pro Asn Asn 1		gcg cct cgc gaa Ala Pro Arg Glu	
		cgt cta ctg ggt Arg Leu Leu Gly 445	Gln Ser Ser
	Leu Val Ala	aat cag ttt gga Asn Gln Phe Gly 460	
		att ctg gca gtg Ile Leu Ala Val 475	

1485

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485

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_	_			_	_		_	gct Ala	_	-			_	_		624
								atg Met								672
	_	-	_				_	tcc Ser	_	_		~	_	_		720
	_				_	_		atg Met					-	_	~ ~	768
								acg Thr 265								816
								gaa Glu								864
								aaa Lys								912
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							Met	acc Thr 345								1056
								gca Ala								1104
								gat Asp								1152
								ctc Leu								1200
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ccg	çag	cgc	ttg	atc	gcc	ggg	atc	ttg	cca	gat	ctg	ctg	gtg	aaa	ggc	1296

Pro	Gln	Arg	Leu 420	Ile	Ala	Gly	Ile	Leu 425	Pro	Asp	Leu	Leu	Val 430	Lys	Gly	
ggc Gly	gac Asp	tat Tyr 435	aaa Lys	cca Pro	gaa Glu	gag Glu	att Ile 440	gcc Ala	Gly 999	agt Ser	aaa Lys	gaa Glu 445	gtc Val	tgg Trp	gcc Ala	1344
aac Asn	ggt Gly 450	ggc ggc	gaa Glu	gtg Val	ttg Leu	gtg Val 455	ctc Leu	aac Asn	ttt Phe	gaa Glu	gac Asp 460	ggt Gly	tgc Cys	tcg Ser	acg Thr	1392
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			ctt Leu													144
			tgg Trp													192
			cat His													240
			gcc Ala													288
			cgc Arg 100													336
	_		ttg Leu	_	-		-		_			_	_		_	384
		_	gac Asp		_		_	-	_	-	-				_	432

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						gaa Glu										480
	_	_				gag Glu	_					-		_	_	528
						cat His										576
						ttt Phe										624
						cag Gln 215										672
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	_	_	_		_	ctg Leu	_	_		_		_	_			864
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_	_		_	_	_	ggt Gly	_		_						-	960
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						ctg Leu										1104
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				gcg Ala												2016
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				acg Thr												2256
				ccg Pro												2304
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				cgt Arg		Arg	Val	Val	Tyr	Gly		Pro	Gln			2400
				gca Ala 805												2448
				caa Gln												2496
				aat Asn												2544
gaa Glu	850 Gly GGG	gga Gly	att Ile	acc Thr	gat Asp	atc Ile 855	gaa Glu	ttt Phe	att Ile	acc Thr	caa Gln 860	tat Tyr	ctg Leu	gtg Val	ttg Leu	2592
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gcg atg gcg ctg acc cgt gct tac act acg ctt cgc gat gaa ctt cat Ala Met Ala Leu Thr Arg Ala Tyr Thr Thr Leu Arg Asp Glu Leu His 900 905 910	2736
cat ctg gca tta cag gaa ttg ccg ggc cat gtg tcg gag gat tgc ttc His Leu Ala Leu Gln Glu Leu Pro Gly His Val Ser Glu Asp Cys Phe 915 920 925	2784
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atg gct cag gaa atc gaa tta aag ttt att gtt aat cac agt gcc gtt Met Ala Gln Glu Ile Glu Leu Lys Phe Ile Val Asn His Ser Ala Val	48 96
atg gct cag gaa atc gaa tta aag ttt att gtt aat cac agt gcc gtt Met Ala Gln Glu Ile Glu Leu Lys Phe Ile Val Asn His Ser Ala Val  1 5 10 15  gag gcg ttg cgt gac cat ctc aat acg ctg ggc ggc gag cac cat gac Glu Ala Leu Arg Asp His Leu Asn Thr Leu Gly Gly Glu His His Asp	
atg gct cag gaa atc gaa tta aag ttt att gtt aat cac agt gcc gtt  Met Ala Gln Glu Ile Glu Leu Lys Phe Ile Val Asn His Ser Ala Val  1 5 10 15  gag gcg ttg cgt gac cat ctc aat acg ctg ggc ggc gag cac cat gac Glu Ala Leu Arg Asp His Leu Asn Thr Leu Gly Gly Glu His His Asp  20 25 30  ccc gtg cag ttg ctg aat att tac tac gaa acg ccg gat aac tgg ctg Pro Val Gln Leu Leu Asn Ile Tyr Tyr Glu Thr Pro Asp Asn Trp Leu	96
atg gct cag gaa atc gaa tta aag ttt att gtt aat cac agt gcc gtt Met Ala Gln Glu Ile Glu Leu Lys Phe Ile Val Asn His Ser Ala Val  1 5 10 15  gag gcg ttg cgt gac cat ctc aat acg ctg ggc ggc gag cac cat gac Glu Ala Leu Arg Asp His Leu Asn Thr Leu Gly Gly Glu His His Asp 20 25 30  ccc gtg cag ttg ctg aat att tac tac gaa acg ccg gat aac tgg ctg Pro Val Gln Leu Leu Asn Ile Tyr Tyr Glu Thr Pro Asp Asn Trp Leu 35 40 45  cgt ggg cac gat atg ggc tta cgt att cgt ggc gaa aac ggt cgc tat Arg Gly His Asp Met Gly Leu Arg Ile Arg Gly Glu Asn Gly Arg Tyr	96
atg gct cag gaa atc gaa tta aag ttt att gtt aat cac agt gcc gtt Met Ala Gln Glu Ile Glu Leu Lys Phe Ile Val Asn His Ser Ala Val  1 5 10 15  gag gcg ttg cgt gac cat ctc aat acg ctg ggc ggc gag cac cat gac Glu Ala Leu Arg Asp His Leu Asn Thr Leu Gly Gly Glu His His Asp 20 25 30  ccc gtg cag ttg ctg aat att tac tac gaa acg ccg gat aac tgg ctg Pro Val Gln Leu Leu Asn Ile Tyr Tyr Glu Thr Pro Asp Asn Trp Leu 35 40 45  cgt ggg cac gat atg ggc tta cgt att cgt ggc gaa aac ggt cgc tat Arg Gly His Asp Met Gly Leu Arg Ile Arg Gly Glu Asn Gly Arg Tyr 50 55 60  gag atg acc atg aaa gtt gca gga aga gtg aca ggc ggc tta cat cag Glu Met Thr Met Lys Val Ala Gly Arg Val Thr Gly Gly Leu His Gln	96 144 192

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		ggc Gly 195												624
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		agc Ser												816
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		att Ile												912
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90

Phe Arg Ile Leu Asn Ala Ser Lys Gly Pro Ala Val Arg Ala Thr Arg

85

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_	_	 _	_			999 Gly 200			_	_		-	_	_	624
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						aat Asn									720
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_		_	_	_		atg Met		_				_		_	816
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						ttc Phe									912
	_		_		Gly	atc Ile			_	_	_		_		960
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	cgt Arg	_			_				_			_		_	_	1056
	aaa Lys															1104
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	gaa Glu															1344
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	ttt Phe															1440
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			cgc Arg													288
			100 GJ <i>Å</i> 333													336
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	_	_		gat Asp	_	-			_		_					192
_		_		gtc Val	_			-	-	_	_			_		240
				atc Ile 85												288
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										gag Glu 235						720
										aaa Lys						768
										ggc Gly						816
			_			_				gtc Val			-	_		864
										tac Tyr						912
										gaa Glu 315						960
										tat Tyr						1008
										gta Val						1056
										Gly						1104
										att Ile						1152
Lys	Thr	Pro	Ser	Met	Glu	Gln	Ala	Ile	Gly	ctg Leu 395	Leu	Ser	Gly	Gly		1200
										atg Met						1248
										gat Asp						1296
										gcc Ala						1344
_	_			_	_	_		_	_	tta Leu		_	_	_	_	1392

atc atc gto Ile Ile Val 465					Glu Phe			1440					
cag gcc acc Gln Ala Thr		Val Leu						1488					
cgc gtg aat Arg Val Asn								1506					
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att ctc cag Ile Leu Gln 50								192					
ctg gtg atc Leu Val Ile 65								240					
gcg ctg acc Ala Leu Thr								288					
gcg ctg gtg Ala Leu Val								336					
gcg gta acc Ala Val Thr 115	Gly Val							384					
gct acg ctg Ala Thr Leu 130								432					
acc aac ggt Thr Asn Gly								480					

145		•			150					155				160	
				ggt Gly 165											528
				att Ile											576
				cgt Arg											<b>624</b>
_	_			ggt Gly			_						_		672
		-		ctg Leu	_	-	_	_	_			_			720
				gca Ala 245											768
				gtg Val											816
	_		_	ely aaa	_	_			_						864
				aat Asn											912
				gtg Val											960
cag Gln	taa *														966
<213 <213	D> 28 L> 89 2> Di 3> Es	91 NA	richi	ia co	oli										
	0> L> CI 2> (1	_	. (891	L)											
atg		atg		aaa Lys 5											48

gcc Ala	acc Thr	gtc Val	agt Ser 20	gcg Ala	aat Asn	geg Ala	atg Met	gca Ala 25	aaa Lys	gac Asp	acc Thr	atc Ile	gcg Ala 30	ctg Leu	gtg Val	96
													gat Asp			144
													ctg Leu			192
cag Gln 65	aac Asn	aac Asn	ccg Pro	gcg Ala	aaa Lys 70	gag Glu	ctg Leu	gcg Ala	aac Asn	gtg Val 75	cag Gln	gac Asp	tta Leu	acc Thr	gtt Val 80	240
													gac Asp			288
ggt Gly	aat Asn	gct Ala	gtg Val 100	aag Lys	atg Met	gct Ala	aac Asn	cag Gln 105	gcg Ala	aac Asn	atc Ile	ccg Pro	gtt Val 110	atc Ile	act Thr	336
	_	_	_	_	_			_		_	_		att Ile	_		384
							Ile						gcg Ala			432
													gct Ala			480
													gtt Val		Ala	528
													gat Asp 190			576
													ccg Pro			624
													gcg Ala			672
													gga Gly			720
													cta Leu			768
act	atc	gct	cag	cta	ccc	gat	cag	att	ggc	gcg	aaa	ggc	gtc	gaa	acc	816

Thr Ile Ala Gln Leu Pro Asp Gln Ile Gly Ala Lys Gly Val Glu Thr 265 gea gat aaa gtg etg aaa gge gag aaa gtt eag get aag tat eeg gtt 864 Ala Asp Lys Val Leu Lys Gly Glu Lys Val Gln Ala Lys Tyr Pro Val 280 gat ctg aaa ctg gtt gtt aag cag tag 891 Asp Leu Lys Leu Val Val Lys Gln * <210> 286 <211> 930 <212> DNA <213> Escherichia coli <220> <221> CDS <222> (1)...(930) <400> 286 atg caa aac gca ggc agc ctc gtt gtt ctt ggc agc att aat gct gac Met Gln Asn Ala Gly Ser Leu Val Val Leu Gly Ser Ile Asn Ala Asp 10 cac att ctt aat ctt caa tct ttt cct act cca ggc gaa acc gta acc 96 His Ile Leu Asn Leu Gln Ser Phe Pro Thr Pro Gly Glu Thr Val Thr 20 25 ggt aac cac tat cag gtt gca ttt ggc ggc aaa ggc gcg aat cag gct 144 Gly Asn His Tyr Gln Val Ala Phe Gly Gly Lys Gly Ala Asn Gln Ala gtg gct gct ggg cgt agc ggt gcg aat atc gcg ttt att gcc tgt acg 192 Val Ala Ala Gly Arg Ser Gly Ala Asn Ile Ala Phe Ile Ala Cys Thr ggt gat gac agc att ggt gag agc gtt cgc cag cag ctc gcc act gat Gly Asp Asp Ser Ile Gly Glu Ser Val Arg Gln Gln Leu Ala Thr Asp aac att gat att act ceg gte age gtg ate aaa gge gaa tea aca ggt 288 Asn Ile Asp Ile Thr Pro Val Ser Val Ile Lys Gly Glu Ser Thr Gly 85 90 gtg gcg ctg att ttt gtt aat ggc gaa ggt gag aat gtc atc ggt att 336 Val Ala Leu Ile Phe Val Asn Gly Glu Gly Glu Asn Val Ile Gly Ile 100 cat gcc ggc gct aat gct gcc ctt tcc ccg gcg ctg gtg gaa gcg caa 384 His Ala Gly Ala Asn Ala Ala Leu Ser Pro Ala Leu Val Glu Ala Gln 115 120 egt gag egt att gee aac geg tea gea tta tta atg cag etg gaa tea 432 Arg Glu Arg Ile Ala Asn Ala Ser Ala Leu Leu Met Gln Leu Glu Ser 130 135 140 cca ctc gaa agt gtg atg gca gcg gcg aaa atc gcc cat caa aat aag 480 Pro Leu Glu Ser Val Met Ala Ala Ala Lys Ile Ala His Gln Asn Lys 145 150 155

act atc gtt gcg ct Thr Ile Val Ala Le	u Asn Pro Ala										
ctg ctg gcg ctg gt Leu Leu Ala Leu Va 180	g gac att att il Asp Ile Ile	acg cca aac gaa a Thr Pro Asn Glu ' 185	acg gaa gca gaa 576 Thr Glu Ala Glu 190								
aag ctc acc ggt at Lys Leu Thr Gly I 195	t cgt gtt gaa e Arg Val Glu 200	Asn Asp Glu Asp	gca gcg aag gcg 624 Ala Ala Lys Ala 205								
gcg cag gta ctg ca Ala Gln Val Leu H 210	at gaa aaa ggt is Glu Lys Gly 215	atc cgt act gta Ile Arg Thr Val : 220	ctg att act tta 672 Leu Ile Thr Leu								
gga agt cgt ggt gg Gly Ser Arg Gly Va 225	ta tgg gct agc al Trp Ala Ser 230	gtg aat ggt gaa g Val Asn Gly Glu 235	ggt cag cgc gtt 720 Gly Gln Arg Val 240								
cct gga ttc cgg g Pro Gly Phe Arg Va 24	al Gln Ala Val	gat acc att gct Asp Thr Ile Ala 250	gcc gga gat acc 768 Ala Gly Asp Thr. 255								
ttt aac ggt gcg t Phe Asn Gly Ala L 260	ta atc acg gca eu Ile Thr Ala	ttg ctg gaa gaa Leu Leu Glu Glu 265	aaa cca ttg cca 816 Lys Pro Leu Pro 270								
gag gcg att cgt to Glu Ala Ile Arg Pi 275	tt gcc cat gct ne Ala His Ala 280	Ala Ala Ala Ile	gcc gta aca cgt 864 Ala Val Thr Arg 285								
aaa ggc gca caa c Lys Gly Ala Gln P 290	ct too gta cog ro Ser Val Pro 295	tgg cgt gaa gag Trp Arg Glu Glu 300	atc gac gca ttt 912 Ile Asp Ala Phe								
tta gac agg cag ag Leu Asp Arg Gln A 305			930								
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<400> 287 Met Lys Val Arg A	la Ser Val Lys	Lys Leu Cys Arg	Asn Cys Lys Ile								
1 Val Lys Arg Asp G	5 ly Val Ile Arg	10 Val Ile Cys Ser	15 Ala Glu Pro Lys								
20 His Lys Gln Arg G 35	ln Gly	25	30								
<210> 288 <211> 443 <212> PRT <213> Escherichia	coli										

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<210> 289 <211> 144

PCT/US00/34419 WO 01/48209

<212> PRT

<213> Escherichia coli

<400> 289

Met Arg Leu Asn Thr Leu Ser Pro Ala Glu Gly Ser Lys Lys Ala Gly 5 10 Lys Arg Leu Gly Arg Gly Ile Gly Ser Gly Leu Gly Lys Thr Gly Gly 25 Arg Gly His Lys Gly Gln Lys Ser Arg Ser Gly Gly Val Arg Arg . 45 40 Gly Phe Glu Gly Gln Met Pro Leu Tyr Arg Arg Leu Pro Lys Phe 60 Gly Phe Thr Ser Arg Lys Ala Ala Ile Thr Ala Glu Ile Arg Leu Ser 70 75 Asp Leu Ala Lys Val Glu Gly Gly Val Val Asp Leu Asn Thr Leu Lys 90 85 Ala Ala Asn Ile Ile Gly Ile Gln Ile Glu Phe Ala Lys Val Ile Leu 105 Ala Gly Glu Val Thr Pro Val Thr Val Arg Gly Leu Arg Val Thr 115 120

Lys Gly Ala Arg Ala Ala Ile Glu Ala Ala Gly Gly Lys Ile Glu Glu

135

<210> 290

<211> 59

<212> PRT

<213> Escherichia coli

<400> 290

Met Ala Lys Thr Ile Lys Ile Thr Gln Thr Arg Ser Ala Ile Gly Arg 10 Leu Pro Lys His Lys Ala Thr Leu Leu Gly Leu Gly Leu Arg Arg Ile 25 Gly His Thr Val Glu Arg Glu Asp Thr Pro Ala Ile Arg Gly Met Ile 40 Asn Ala Val Ser Phe Met Val Lys Val Glu Glu ຸ 55

<210> 291

<211> 167

<212> PRT

<213> Escherichia coli

<400> 291

Met Ala His Ile Glu Lys Gln Ala Gly Glu Leu Gln Glu Lys Leu Ile 10 Ala Val Asn Arg Val Ser Lys Thr Val Lys Gly Gly Arg Ile Phe Ser 25 Phe Thr Ala Leu Thr Val Val Gly Asp Gly Asn Gly Arg Val Gly Phe 40 Gly Tyr Gly Lys Ala Arg Glu Val Pro Ala Ala Ile Gln Lys Ala Met 55 60 Glu Lys Ala Arg Arg Asn Met Ile Asn Val Ala Leu Asn Asn Gly Thr 70 75 Leu Gln His Pro Val Lys Gly Val His Thr Gly Ser Arg Val Phe Met 90 Gln Pro Ala Ser Glu Gly Thr Gly Ile Ile Ala Gly Gly Ala Met Arg 105 Ala Val Leu Glu Val Ala Gly Val His Asn Val Leu Ala Lys Ala Tyr

<210> 292 <211> 117 <212> PRT <213> Escherichia coli

<400> 292

 Met
 Asp
 Lys
 Lys
 Ser
 Ala
 Arg
 Ile
 Arg
 Arg
 Ala
 Thr
 Arg
 Ala
 Thr
 Arg
 Ile
 Ile
 Ile
 Ile
 Ile
 Ile
 Ile
 Val
 Ilis
 Arg
 Ile
 Ile
 Val
 Ile
 Val</t

<210> 293 <211> 177 <212> PRT <213> Escherichia coli

<400> 293

Met Ser Arg Val Ala Lys Ala Pro Val Val Pro Ala Gly Val Asp 5 10 Val Lys Ile Asn Gly Gln Val Ile Thr Ile Lys Gly Lys Asn Gly Glu 25 Leu Thr Arg Thr Leu Asn Asp Ala Val Glu Val Lys His Ala Asp Asn 40 Thr Leu Thr Phe Gly Pro Arg Asp Gly Tyr Ala Asp Gly Trp Ala Gln 55 Ala Gly Thr Ala Arg Ala Leu Leu Asn Ser Met Val Ile Gly Val Thr 70 75 Glu Gly Phe Thr Lys Lys Leu Gln Leu Val Gly Val Gly Tyr Arg Ala 90 Ala Val Lys Gly Asn Val Ile Asn Leu Ser Leu Gly Phe Ser His Pro 105 Val Asp His Gln Leu Pro Ala Gly Ile Thr Ala Glu Cys Pro Thr Gln 120 Thr Glu Ile Val Leu Lys Gly Ala Asp Lys Gln Val Ile Gly Gln Val 135 140 Ala Ala Asp Leu Arg Ala Tyr Arg Arg Pro Glu Pro Tyr Lys Gly Lys 150 155 Gly Val Arg Tyr Ala Asp Glu Val Val Arg Thr Lys Glu Ala Lys Lys 165 170

Lys

<210> 294 <211> 130 <212> PRT <213> Escherichia coli <400> 294 Met Ser Met Gln Asp Pro Ile Ala Asp Met Leu Thr Arg Ile Arg Asn 10 Gly Gln Ala Ala Asn Lys Ala Ala Val Thr Met Pro Ser Ser Lys Leu Lys Val Ala Ile Ala Asn Val Leu Lys Glu Glu Gly Phe Ile Glu Asp Phe Lys Val Glu Gly Asp Thr Lys Pro Glu Leu Glu Leu Thr Leu Lys 55 Tyr Phe Gln Gly Lys Ala Val Val Glu Ser Ile Gln Arg Val Ser Arg 70 Pro Gly Leu Arg Ile Tyr Lys Arg Lys Asp Glu Leu Pro Lys Val Met 90 Ala Gly Leu Gly Ile Ala Val Val Ser Thr Ser Lys Gly Val Met Thr 105 Asp Arg Ala Ala Arg Gln Ala Gly Leu Gly Gly Glu Ile Ile Cys Tyr 120 Val Ala 130 <210> 295 <211> 101 <212> PRT <213> Escherichia coli <400> 295 Met Ala Lys Gln Ser Met Lys Ala Arg Glu Val Lys Arg Val Ala Leu 1 5 10 Ala Asp Lys Tyr Phe Ala Lys Arg Ala Glu Leu Lys Ala Ile Ile Ser . 25 20 Asp Val Asn Ala Ser Asp Glu Asp Arg Trp Asn Ala Val Leu Lys Leu 40 Gln Thr Leu Pro Arg Asp Ser Ser Pro Ser Arg Gln Arg Asn Arg Cys 55 Arg Gln Thr Gly Arg Pro His Gly Phe Leu Arg Lys Phe Gly Leu Ser 70 75 Arg Ile Lys Val Arg Glu Ala Ala Met Arg Gly Glu Ile Pro Gly Leu 85 Lys Lys Ala Ser Trp 100 <210> 296 <211> 179 <212> PRT <213> Escherichia coli <400> 296

15

. 10

Met Ala Lys Leu His Asp Tyr Tyr Lys Asp Glu Val Val Lys Lys Leu

Met Thr Glu Phe Asn Tyr Asn Ser Val Met Gln Val Pro Arg Val Glu

20 25 Lys Ile Thr Leu Asn Met Gly Val Gly Glu Ala Ile Ala Asp Lys Lys 40 Leu Leu Asp Asn Ala Ala Ala Asp Leu Ala Ala Ile Ser Gly Gln Lys 55 Pro Leu Ile Thr Lys Ala Arg Lys Ser Val Ala Gly Phe Lys Ile Arg 70 75 Gln Gly Tyr Pro Ile Gly Cys Lys Val Thr Leu Arg Gly Glu Arg Met 85 90 Trp Glu Phe Phe Glu Arg Leu Ile Thr Ile Ala Val Pro Arg Ile Arg 100 105 Asp Phe Arg Gly Leu Ser Ala Lys Ser Phe Asp Gly Arg Gly Asn Tyr 120 115 125 Ser Met Gly Val Arg Glu Gln Ile Ile Phe Pro Glu Ile Asp Tyr Asp 135 140 Lys Val Asp Arg Val Arg Gly Leu Asp Ile Thr Ile Thr Thr Thr Ala 150 155 Lys Ser Asp Glu Glu Gly Arg Ala Leu Leu Ala Ala Phe Asp Phe Pro Phe Arg Lys

<210> 297 <211> 104 <212> PRT

<213> Escherichia coli

<400> 297

Met Ala Ala Lys Ile Arg Arg Asp Asp Glu Val Ile Val Leu Thr Gly 10 Lys Asp Lys Gly Lys Arg Gly Lys Val Lys Asn Val Leu Ser Ser Gly Lys Val Ile Val Glu Gly Ile Asn Leu Val Lys Lys Ris Gln Lys Pro Val Pro Ala Leu Asn Gln Pro Gly Gly Ile Val Glu Lys Glu Ala Ala 55 Ile Gln Val Ser Asn Val Ala Ile Phe Asn Ala Ala Thr Gly Lys Ala 70 75 Asp Arg Val Gly Phe Arg Phe Glu Asp Gly Lys Lys Val Arg Phe Phe 85 90 Lys Ser Asn Ser Glu Thr Ile Lys

100

<210> 298 <211> 123 <212> PRT <213> Escherichia coli

Met Ile Gln Glu Gln Thr Met Leu Asn Val Ala Asp Asn Ser Gly Ala 10 Arg Arg Val Met Cys Ile Lys Val Leu Gly Gly Ser His Arg Arg Tyr Ala Gly Val Gly Asp Ile Ile Lys Ile Thr Ile Lys Glu Ala Ile Pro 40 Arg Gly Lys Val Lys Lys Gly Asp Val Leu Lys Ala Val Val Arg 55 Thr Lys Lys Gly Val Arg Arg Pro Asp Gly Ser Val Ile Arg Phe Asp

Gly Asn Ala Cys Val Leu Leu Asn Asn Asn Ser Glu Gln Pro Ile Gly
85 90 95

Thr Arg Ile Phe Gly Pro Val Thr Arg Glu Leu Arg Ser Glu Lys Phe
100 105 110

Met Lys Ile Ile Ser Leu Ala Pro Glu Val Leu
115 120

<210> 299 <211> 485 <212> PRT <213> Escherichia coli

<400> 299

Met Gly Ile Tyr Phe Thr Asn Ser Asp Asp Gln Ile Tyr Phe Lys Arg Ser Glu Gly Met Ser Asp Ile Asn His Ala Gly Ser Asp Leu Ile Phe 25 Glu Leu Glu Asp Arg Pro Pro Phe His Gln Ala Leu Val Gly Ala Ile 40 Thr His Leu Leu Ala Ile Phe Val Pro Met Val Thr Pro Ala Leu Ile 55 Val Gly Ala Ala Leu Gln Leu Ser Ala Glu Thr Thr Ala Tyr Leu Val 70 75 Ser Met Ala Met Ile Ala Ser Gly Ile Gly Thr Trp Leu Gln Val Asn 85 90 Arg Tyr Gly Ile Val Gly Ser Gly Leu Leu Ser Ile Gln Ser Val Asn 105 Phe Ser Phe Val Thr Val Met Ile Ala Leu Gly Ser Ser Met Lys Ser 120 Asp Gly Phe His Glu Glu Leu Ile Met Ser Ser Leu Leu Gly Val Ser 135 Phe Val Gly Ala Phe Leu Val Val Gly Ser Ser Phe Ile Leu Pro Tyr 155 150 Leu Arg Arg Val Ile Thr Pro Thr Val Ser Gly Ile Val Val Leu Met 170 Ile Gly Leu Ser Leu Ile Lys Val Gly Ile Ile Asp Phe Gly Gly Gly 185 Phe Ala Ala Lys Ser Ser Gly Thr Phe Gly Asn Tyr Glu His Leu Gly 200 205 Val Gly Leu Leu Val Leu Ile Val Val Ile Gly Phe Asn Cys Cys Arg Ser Pro Leu Leu Arg Met Gly Gly Ile Ala Ile Gly Leu Cys Val Gly 235 240 230 Tyr Ile Ala Ser Leu Cys Leu Gly Met Val Asp Phe Ser Ser Met Arg 250 Asn Leu Pro Leu Ile Thr Ile Pro His Pro Phe Lys Tyr Gly Phe Ser 265 Phe Ser Phe His Gln Phe Leu Val Val Gly Thr Ile Tyr Leu Leu Ser 280 285 Val Leu Glu Ala Val Gly Asp Ile Thr Ala Thr Ala Met Val Ser Arg 290 295 300 Arg Pro Ile Gln Gly Glu Glu Tyr Gln Ser Arg Leu Lys Gly Gly Val 315 320 310 Leu Ala Asp Gly Leu Val Ser Val Ile Ala Ser Ala Val Gly Ser Leu 325 330 Pro Leu Thr Thr Phe Ala Gln Asn Asn Gly Val Ile Gln Met Thr Gly 345 Val Ala Ser Arg Tyr Val Gly Arg Thr Ile Ala Val Met Leu Val Ile 360 Leu Gly Leu Phe Pro Met Ile Gly Gly Phe Phe Thr Thr Ile Pro Ser

375 380 Ala Val Leu Gly Gly Ala Met Thr Leu Met Phe Ser Met Ile Ala Ile 395 390 Ala Gly Ile Arg Ile Ile Ile Thr Asn Gly Leu Lys Arg Arg Glu Thr 405 410 Leu Ile Val Ala Thr Ser Leu Gly Leu Gly Leu Gly Val Ser Tyr Asp 425 420 Pro Glu Ile Phe Lys Ile Leu Pro Ala Ser Ile Tyr Val Leu Val Glu 435 440 Asn Pro Ile Cys Ala Gly Gly Leu Thr Ala Ile Leu Leu Asn Ile Ile 455 460 Leu Pro Gly Gly Tyr Arg Gln Glu Asn Val Leu Pro Gly Ile Thr Ser 475 Ala Glu Glu Met Asp

<210> 300 <211> 439 <212> PRT

<213> Escherichia coli

<400> 300

Met Met Ser Gly Glu His Thr Leu Lys Ala Val Arg Gly Ser Phe Ile Asp Val Thr Arg Thr Ile Asp Asn Pro Glu Glu Ile Ala Ser Ala Leu 25 Arg Phe Ile Glu Asp Gly Leu Leu Leu Ile Lys Gln Gly Lys Val Glu 40 Trp Phe Gly Glu Trp Glu Asn Gly Lys His Gln Ile Pro Asp Thr Ile 55 Arg Val Arg Asp Tyr Arg Gly Lys Leu Ile Val Pro Gly Phe Val Asp 70 75 Thr His Ile His Tyr Pro Gln Ser Glu Met Val Gly Ala Tyr Gly Glu 90 Gln Leu Leu Glu Trp Leu Asn Lys His Thr Phe Pro Thr Glu Arg Arg 105 Tyr Glu Asp Leu Glu Tyr Ala Arg Glu Met Ser Ala Phe Phe Ile Lys 120 Gln Leu Leu Arg Asn Gly Thr Thr Thr Ala Leu Val Phe Gly Thr Val 135 140 His Pro Gln Ser Val Asp Ala Leu Phe Glu Ala Ala Ser His Ile Asn 150 155 Met Arg Met Ile Ala Gly Lys Val Met Met Asp Arg Asn Ala Pro Asp 165 170 Tyr Leu Leu Asp Thr Ala Glu Ser Ser Tyr His Gln Ser Lys Glu Leu 185 Ile Glu Arg Trp His Lys Asn Gly Arg Leu Leu Tyr Ala Ile Thr Pro 200 Arg Phe Ala Pro Thr Ser Pro Glu Gln Met Ala Met Ala Gln Arg 215 220 Leu Lys Glu Glu Tyr Pro Asp Thr Trp Val His Thr His Leu Cys Glu 235 230 Asn Lys Asp Glu Ile Ala Trp Val Lys Ser Leu Tyr Pro Asp His Asp 245 250 Gly Tyr Leu Asp Val Tyr His Gln Tyr Gly Leu Thr Gly Lys Asn Cys 265 Val Phe Ala His Cys Val His Leu Glu Glu Lys Glu Trp Asp Arg Leu 280 285 Ser Glu Thr Lys Ser Ser Ile Ala Phe Cys Pro Thr Ser Asn Leu Tyr 295

Leu Gly Ser Gly Leu Phe Asn Leu Lys Lys Ala Trp Gln Lys Lys Val 310 315 Lys Val Gly Met Gly Thr Asp Ile Gly Ala Gly Thr Thr Phe Asn Met 330 325 Leu Gln Thr Leu Asn Glu Ala Tyr Lys Val Leu Gln Leu Gln Gly Tyr 340 345 Arg Leu Ser Ala Tyr Glu Ala Phe Tyr Leu Ala Thr Leu Gly Gly Ala 360 Lys Ser Leu Gly Leu Asp Asp Leu Ile Gly Asn Phe Leu Pro Gly Lys 375 380 Glu Ala Asp Phe Val Val Met Glu Pro Thr Ala Thr Pro Leu Gln Gln 390 395 400 Leu Arg Tyr Asp Asn Ser Val Ser Leu Val Asp Lys Leu Phe Val Met 405 410 Met Thr Leu Gly Asp Asp Arg Ser Ile Tyr Arg Thr Tyr Val Asp Gly 420 425 Arg Leu Val Tyr Glu Arg Asn 435

<210> 301 <211> 189

<212> PRT

<213> Escherichia coli

<400> 301

Met Ser Gly Asp Ile Leu Gln Thr Pro Asp Ala Pro Lys Pro Gln Gly 10 Ala Leu Asp Asn Tyr Phe Lys Ile Thr Ala Arg Gly Ser Thr Val Arg 25 Gln Glu Val Leu Ala Gly Leu Thr Thr Phe Leu Ala Met Val Tyr Ser 40 Val Ile Val Val Pro Gly Met Leu Gly Lys Ala Gly Phe Pro Pro Ala 55 Ala Val Phe Val Ala Thr Cys Leu Val Ala Gly Phe Gly Ser Leu Leu 70 Met Gly Leu Trp Ala Asn Leu Pro Met Ala Ile Gly Cys Ala Ile Ser 85 90 Leu Thr Ala Phe Thr Ala Phe Ser Leu Val Leu Gly Gln Gln Ile Ser 105 Val Pro Val Ala Leu Gly Ala Val Phe Leu Met Gly Val Ile Phe Thr 120 Ala Ile Ser Val Thr Gly Val Arg Thr Trp Ile Leu Arg Asn Leu Pro 135 Met Gly Ile Ala His Gly Thr Gly Ile Gly Ile Gly Leu Phe Leu Leu 150 Leu Ile Ala Ala Asn Gly Val Gly Met Val Ile Lys Asn Pro Ile Glu 170 Gly Leu Gln Trp Arg Ser Val Arg Leu Pro Pro Ser Arg

<210> 302

<211> 276

<212> PRT

<213> Escherichia coli

<400> 302

Met Ala Leu Gly Ala Phe Thr Ser Phe Pro Val Met Met Ser Leu Leu 1 5 10 15 Gly Leu Ala Val Ile Phe Gly Leu Glu Lys Cys Arg Val Pro Gly Gly

25 Ile Leu Leu Val Ile Ile Ala Ile Ser Ile Ile Gly Leu Ile Phe Asp 40 Pro Ala Val Lys Tyr His Gly Leu Val Ala Met Pro Ser Leu Thr Gly 55 60 Glu Asp Gly Lys Ser Leu Ile Phe Ser Leu Asp Ile Met Gly Ala Leu 70 75 Gln Pro Thr Val Leu Pro Ser Val Leu Ala Leu Val Met Thr Ala Val 85 90 Phe Asp Ala Thr Gly Thr Ile Arg Ala Val Ala Gly Gln Ala Asn Leu 105 Leu Asp Lys Asp Asn Gln Ile Ile Asn Gly Gly Lys Ala Leu Thr Ser 120 125 Asp Ser Val Ser Ser Ile Phe Ser Gly Leu Val Gly Ala Ala Pro Ala 135 140 Ala Val Tyr Ile Glu Ser Ala Ala Gly Thr Ala Ala Gly Gly Lys Thr 150 155 Gly Leu Thr Ala Thr Val Val Gly Ala Leu Phe Leu Leu Ile Leu Phe 165 170 Leu Ser Pro Leu Ser Phe Leu Ile Pro Gly Tyr Ala Thr Ala Pro Ala 185 Leu Met Tyr Val Gly Leu Leu Met Leu Ser Asn Val Ser Lys Leu Asp 200 Phe Asn Asp Phe Ile Asp Ala Met Ala Gly Leu Val Cys Ala Val Phe 215 220 Ile Val Leu Thr Cys Asn Ile Val Thr Gly Ile Met Leu Gly Phe Val 230 235 Thr Leu Val Val Gly Arg Val Phe Ala Arg Glu Trp Gln Lys Leu Asn 250 245 Ile Gly Thr Val Ile Ile Thr Ala Ala Leu Val Ala Phe Tyr Ala Gly 260 265 Gly Trp Ala Ile 275

<210> 303 <211> 466

<212> PRT

<213> Escherichia coli

<400> 303

Met Asn Ser Glu Gly Gly Lys Pro Gly Asn Val Leu Thr Val Asn Gly 10 Asn Tyr Thr Gly Asn Asn Gly Leu Met Thr Phe Asn Ala Thr Leu Gly 25 Gly Asp Asn Ser Pro Thr Asp Lys Met Asn Val Lys Gly Asp Thr Gln 40 Gly Asn Thr Arg Val Arg Val Asp Asn Ile Gly Gly Val Gly Ala Gln 55 Thr Val Asn Gly Ile Glu Leu Ile Glu Val Gly Gly Asn Ser Ala Gly 70 75 Asn Phe Ala Leu Thr Thr Gly Thr Val Glu Ala Gly Ala Tyr Val Tyr 90 Thr Leu Ala Lys Gly Lys Gly Asn Asp Glu Lys Asn Trp Tyr Leu Thr 105 110 Ser Lys Trp Asp Gly Val Thr Pro Ala Asp Thr Pro Asp Pro Ile Asn 125 120 Asn Pro Pro Val Val Asp Pro Glu Gly Pro Ser Val Tyr Arg Pro Glu 135 140 Ala Gly Ser Tyr Ile Ser Asn Ile Ala Ala Ala Asn Ser Leu Phe Ser 155

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His Arg Leu His Asp Arg Leu Gly Glu Pro Gln Tyr Thr Asp Ser Leu
               165
                                   170
His Ser Gln Gly Ser Ala Ser Ser Met Trp Met Arg His Val Gly Gly
                               185
           180
His Glu Arg Ser Arg Ala Gly Asp Gly Gln Leu Asn Thr Gln Ala Asn
       195
                           200
Arg Tyr Val Leu Gln Leu Gly Gly Asp Leu Ala Gln Trp Ser Ser Asn
                                           220
                       215
Ala Gln Asp Arg Trp His Leu Gly Val Met Ala Gly Tyr Ala Asn Gln
                   230
                                       235
His Ser Asn Thr Gln Ser Asn Arg Val Gly Tyr Lys Ser Asp Gly Arg
               245
                                   250
Ile Ser Gly Tyr Ser Ala Gly Leu Tyr Ala Thr Trp Tyr Gln Asn Asp
                               265
            260
Ala Asn Lys Thr Gly Ala Tyr Val Asp Ser Trp Ala Leu Tyr Asn Trp
                           280
Phe Asp Asn Ser Val Ser Ser Asp Asn Arg Ser Ala Asp Asp Tyr Asp
                       295
Ser Arg Gly Val Thr Ala Ser Val Glu Gly Gly Tyr Thr Phe Glu Ala
                                        315
                   310
Gly Thr Phe Ser Gly Ser Glu Gly Thr Leu Asn Thr Trp Tyr Val Gln
               325
                                   330
Pro Gln Ala Gln Ile Thr Trp Met Gly Val Lys Asp Ser Asp His Thr
                               345
Arg Lys Asp Gly Thr Arg Ile Glu Thr Glu Gly Asp Gly Asn Val Gln
                           360
                                               365
Thr Arg Leu Gly Val Lys Thr Tyr Leu Asn Ser His His Gln Arg Asp
                       375
Asp Gly Lys Gln Arg Glu Phe Gln Pro Tyr Ile Glu Ala Asn Trp Ile
                   390
                                       395
Asn Asn Ser Lys Val Tyr Ala Val Lys Met Asn Gly Gln Thr Val Gly
               405
                                   410
Arg Glu Gly Ala Arg Asn Leu Gly Glu Val Arg Thr Gly Val Glu Ala
                               425
            420
Lys Val Asn Asn Asn Leu Ser Leu Trp Gly Asn Val Gly Val Gln Leu
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Gly Asp Lys Gly Tyr Ser Asp Thr Gln Gly Met Leu Gly Val Lys Tyr
Ser Trp
465
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<210> 304 <211> 1325 <212> PRT <213> Escherichia coli

<400> 304

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 Tyr
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 Val
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 Trp
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 Leu
 Gln
 Val
 Phe

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 Ala
 Cys
 Ser
 Glu
 Leu
 Thr
 Arg
 Ala
 Gly
 Lys
 Thr
 Ser
 Thr
 Val

 Asn
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 Arg
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 Ser
 Ser
 Gly
 Leu
 Thr
 Thr
 Lys
 Phe
 Ser
 Arg
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 Asn
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 Thr
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 Gly
 Ala
 Ser
 Leu
 Thr
 Asn
 Thr
 Asn
 Ala
 Thr
 Thr

			100					105					110		
Ala	Asn	Glu 115	qaA	Ser	Glu	Gly	Thr 120		Asn	Val	Leu	Gly 125		Thr	Trp
Arg	Leu 130	Tyr	Asp	Ser	Gly	Asn 135	Asn	Ala	Arg	Pro	Leu 140	Asn	Val	Gly	Gln
Ser 145	Gly	Thr	Gly	Thr	Leu 150	Asn	Ile	Lys	Gln	Lys 155	Gly	His	Val	Asp	Gly
Gly	Tyr	Leu	Arg	Leu 165	Gly	Ser	Ser	Thr	Gly 170	Gly	Val	Gly	Thr	Val 175	Asn
Val	Glu	Gly	Glu 180	Asp	Ser	Val	Leu	Thr 185	Thr	Glu	Leu	Phe	Glu 190	Ile	Gly
Ser	Tyr	Gly 195	Thr	Gly	Ser	Leu	Asn 200	Ile	Thr	Asp	Lys	Gly 205	Tyr	Val	Thr
	210		Va1			215					220				
225			Glu	_	230	_		_		235	_			_	240
			Phe	245					250					255	
_		_	Gly 260					265					270	_	
		275	Ile				280					285			
	290	_	Arg			295	_	_		_	300	_			
305			Asn	_	310					315	_				320
			Gly	325					330					335	
			Leu 340 Asp					345					350		
		355	_				360					365			
	370		Ile			375					380				
385			Gly	_	390					395		_			400
_	-	_	Gly	405	_				410				_	415	
			420 Ile	_				425	_	-			430		_
		435	Ile			$\sqrt{2}$	440					445			
	450		Phe			455					460				
465	_	_	Gly		470					475			_	-	480
	_		Ile	485					490					495	
Ser	Asn	Gly	500 Ala	Thr	Leu	Asn	Ser	505 Thr	Gly	Tyr	Gly	Phe	510 Ile	Gly	Gly
		515	Gly				520		_	_	_	525		_	_
	530		Thr			535					540				
545			Gly		550					555					560
			Gln	565					570		_			575	
J	- 4-	,	580					585	4			-4	590		- 3

Val Asp Gly Gln Asn Ser Leu Leu Glu Thr Phe Asn Met Tyr Val Gly 600 Thr Ser Gly Thr Gly Thr Leu Thr Leu Thr Asn Asn Gly Thr Leu Asn 615 620 Val Glu Gly Glu Val Tyr Leu Gly Val Phe Glu Pro Ala Val Gly 630 635 Thr Leu Asn Ile Gly Ala Ala His Gly Glu Ala Ala Asp Ala Gly 645 650 Phe Ile Thr Asn Ala Thr Lys Val Glu Phe Gly Leu Gly Glu Gly Val 660 665 Phe Val Phe Asn His Thr Asn Asn Ser Asp Ala Gly Tyr Gln Val Asp 680 Met Leu Ile Thr Gly Asp Asp Lys Asp Gly Lys Val Ile His Asp Ala 695 700 Gly His Thr Val Phe Asn Ala Gly Asn Thr Tyr Ser Gly Lys Thr Leu 710 715 Val Asn Asp Gly Leu Leu Thr Ile Ala Ser His Thr Ala Asp Gly Val 725 730 Thr Gly Met Gly Ser Ser Glu Val Thr Ile Ala Asn Pro Gly Thr Leu 745 Asp Ile Leu Ala Ser Thr Asn Ser Ala Gly Asp Tyr Thr Leu Thr Asn 760 765 Ala Leu Lys Gly Asp Gly Leu Met Arg Val Gln Leu Ser Ser Asp 775 780 Lys Met Phe Gly Phe Thr His Ala Thr Gly Thr Glu Phe Ala Gly Val 790 795 Ala Gln Leu Lys Asp Ser Thr Phe Thr Leu Glu Arg Asp Asn Thr Ala 810 805 Ala Leu Thr His Ala Met Leu Gln Ser Asp Ser Glu Asn Thr Thr Ser 825 820 Val Lys Val Gly Glu Gln Ser Ile Gly Gly Leu Ala Met Asn Gly Gly 840 Thr Ile Ile Phe Asp Thr Asp Ile Pro Ala Ala Thr Leu Ala Glu Gly 860 855 Tyr Ile Ser Val Asp Thr Leu Val Val Gly Ala Gly Asp Tyr Thr Trp 870 875 Lys Gly Arg Asn Tyr Gln Val Asn Gly Thr Gly Asp Val Leu Ile Asp 885 890 Val Pro Lys Pro Trp Asn Asp Pro Met Ala Asn Asn Pro Leu Thr Thr 905 Leu Asn Leu Leu Glu His Asp Asp Ser His Val Gly Val Gln Leu Val 920 Lys Ala Gln Thr Val Ile Gly Ser Gly Gly Ser Leu Thr Leu Arg Asp 935 940 Leu Gln Gly Asp Glu Val Glu Ala Asp Lys Thr Leu His Ile Ala Gln 950 955 Asn Gly Thr Val Val Ala Glu Gly Asp Tyr Gly Phe Arg Leu Thr Thr 970 965 Ala Pro Gly Asn Gly Leu Tyr Val Asn Tyr Gly Leu Lys Ala Leu Asn .985 Ile His Gly Gly Gln Lys Leu Thr Leu Ala Glu His Gly Gly Ala Tyr 1005 1000 Gly Ala Thr Ala Asp Met Ser Ala Lys Ile Gly Gly Glu Gly Asp Leu 1010 1015 1020 Ala Ile Asn Thr Val Arg Gln Val Ser Leu Ser Asn Gly Gln Asn Asp 1030 1035 1040 Tyr Gln Gly Ala Thr Tyr Val Gln Met Gly Thr Leu Arg Thr Asp Ala 1050 1045 Asp Gly Ala Leu Gly Asn Thr Arg Glu Leu Asn Ile Ser Asn Ala Ala 1065 Ile Val Asp Leu Asn Gly Ser Thr Gln Thr Val Glu Thr Phe Thr Gly

1080 1075 1085 Gln Met Gly Ser Thr Val Leu Phe Lys Glu Gly Ala Leu Thr Val Asn 1095 1100 Lys Gly Gly Ile Ser Gln Gly Glu Leu Thr Gly Gly Gly Asn Leu Asn 1110 1115 Val Thr Gly Gly Thr Leu Ala Ile Glu Gly Leu Asn Ala Arg Tyr Asn 1125 1130 Ala Leu Thr Ser Ile Ser Pro Asn Ala Glu Val Ser Leu Asp Asn Thr 1140 1145 Gln Gly Leu Gly Arg Gly Asn Ile Ala Asn Asp Gly Leu Leu Thr Leu 1155 1160 1165 Lys Asn Val Thr Gly Glu Leu Arg Asn Ser Ile Ser Gly Lys Gly Ile 1175 1180 Val Ser Ala Thr Ala Arg Thr Asp Val Glu Leu Asp Gly Asp Asn Ser 1190 1195 Arg Phe Val Gly Gln Phe Asn Ile Asp Thr Gly Ser Ala Leu Ser Val 1205 1210 Asn Glu Gln Lys Asn Leu Gly Asp Ala Ser Val Ile Asn Asn Gly Leu 1220 1225 Leu Thr Ile Ser Thr Glu Arg Ser Trp Ala Met Thr His Ser Ile Ser 1245 1235 1240 Gly Ser Gly Asp Val Thr Lys Leu Gly Thr Gly Ile Leu Thr Leu Asn 1255 1260 Asn Asp Ser Ala Ala Tyr Gln Gly Thr Thr Asp Ile Val Gly Glu 1275 1270 Ile Ala Phe Gly Ser Asp Ser Ala Ile Asn Met Ala Ser Gln His Ile 1285 1290 1295 Asn Ile His Asn Ser Gly Val Met Ser Gly Asn Val Thr Thr Ala Gly 1300 1305 1310 Asp Met Asn Val Met Pro Gly Gly Gly Thr Ala Cys Arg 1320

<210> 305 <211> 251

22117 231

<212> PRT

<213> Escherichia coli

<400> 305

Met Thr Glu Ala Gln Arg His Gln Ile Leu Leu Glu Met Leu Ala Gln 10 5 Leu Gly Phe Val Thr Val Glu Lys Val Val Glu Arg Leu Gly Ile Ser 20 25 Pro Ala Thr Ala Arg Arg Asp Ile Asn Lys Leu Asp Glu Ser Gly Lys 40 Leu Lys Lys Val Arg Asn Gly Ala Glu Ala Ile Thr Gln Gln Arg Pro 55 Arg Trp Thr Pro Met Asn Leu His Gln Ala Gln Asn His Asp Glu Lys 70 75 Val Arq Ile Ala Lys Ala Ala Ser Gln Leu Val Asn Pro Gly Glu Ser Val Val Ile Asn Cys Gly Ser Thr Ala Phe Leu Leu Gly Arg Glu Met 105 Cys Gly Lys Pro Val Gln Ile Ile Thr Asn Tyr Leu Pro Leu Ala Asn 120 Tyr Leu Ile Asp Gln Glu His Asp Ser Val Ile Ile Met Gly Gly Gln 135 140 Tyr Asn Lys Ser Gln Ser Ile Thr Leu Ser Pro Gln Gly Ser Glu Asn 150 155 Ser Leu Tyr Ala Gly His Trp Met Phe Thr Ser Gly Lys Gly Leu Thr 170

<210> 306 <211> 274 <212> PRT <213> Escherichia coli

<400> 306

Met Thr Glu Phe Thr Thr Leu Leu Gln Gln Gly Asn Ala Trp Phe Phe 1 5 10 Ile Pro Ser Ala Ile Leu Leu Gly Ala Leu His Gly Leu Glu Pro Gly 25 His Ser Lys Thr Met Met Ala Ala Phe Ile Ile Ala Ile Lys Gly Thr 35 . 40 Ile Lys Gln Ala Val Met Leu Gly Leu Ala Ala Thr Ile Ser His Thr 55 Ala Val Val Trp Leu Ile Ala Phe Gly Gly Met Val Ile Ser Lys Arg 75 70 Phe Thr Ala Gln Ser Ala Glu Pro Trp Leu Gln Leu Ile Ser Ala Val 85 90 Ile Ile Ile Ser Thr Ala Phe Trp Met Phe Trp Arg Thr Trp Arg Gly 100 105 Glu Arg Asn Trp Leu Glu Asn Met His Gly His Asp Tyr Glu His His 120 His His Asp His Glu His His His Asp His Gly His His His His 135 Glu His Gly Glu Tyr Gln Asp Ala His Ala Arg Ala His Ala Asn Asp 150 155 160 Ile Lys Arg Arg Phe Asp Gly Arg Glu Val Thr Asn Trp Gln Ile Leu 170 175 Leu Phe Gly Leu Thr Gly Gly Leu Ile Pro Cys Pro Ala Ala Ile Thr 180 185 190 Val Leu Leu Ile Cys Ile Gln Leu Lys Ala Leu Thr Leu Gly Ala Thr 200 205 Leu Val Val Ser Phe Ser Ile Gly Leu Ala Leu Thr Leu Val Thr Val 210 215 220 Gly Val Gly Ala Ala Ile Ser Val Gln Gln Val Ala Lys Arg Trp Ser 225 230 235 240 Gly Phe Asn Thr Leu Ala Lys Arg Ala Pro Tyr Phe Ser Ser Leu Leu 245 250 255 Ile Gly Leu Val Gly Val Tyr Met Gly Val His Gly Phe Met Gly Ile 260 265 Met Arg

<210> 307

<211> 172

<212> PRT

<213> Escherichia coli

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<210> 308 <211> 344 <212> PRT

<213> Escherichia coli

<400> 308

Met Glu Ile Arg Ile Met Leu Phe Ile Leu Met Met Val Met Pro 10 Val Ser Tyr Ala Ala Cys Tyr Ser Glu Leu Ser Val Gln His Asn Leu 25 Val Val Gln Gly Asp Phe Ala Leu Thr Gln Thr Gln Met Ala Thr Tyr Glu His Asn Phe Asn Asp Ser Ser Cys Val Ser Thr Asn Thr Ile Thr 55 Pro Met Ser Pro Ser Asp Ile Ile Val Gly Leu Tyr Asn Asp Thr Ile 70 75 Lys Leu Asn Leu His Phe Glu Trp Thr Asn Lys Asn Asn Ile Thr Leu 85 90 Ser Asn Asn Gln Thr Ser Phe Thr Ser Gly Tyr Ser Val Thr Val Thr 100 105 Pro Ala Ala Ser Asn Ala Lys Val Asn Val Ser Ala Gly Gly Gly 120 Ser Val Met Ile Asn Gly Val Ala Thr Leu Ser Ser Ala Ser Ser Ser 140 135 Thr Arg Gly Ser Ala Ala Val Gln Phe Leu Leu Cys Leu Leu Gly Gly 150 155 Lys Ser Trp Asp Ala Cys Val Asn Ser Tyr Arg Asn Ala Leu Ala Gln 165 170 Asn Ala Gly Val Tyr Ser Phe Asn Leu Thr Leu Ser Tyr Asn Pro Ile 185 Thr Thr Cys Lys Pro Asp Asp Leu Leu Ile Thr Leu Asp Ser Ile 200 Pro Val Ser Gln Leu Pro Ala Thr Gly Asn Lys Ala Thr Ile Asn Ser 215 220 Lys Gln Gly Asp Ile Ile Leu Arg Cys Lys Asn Leu Leu Gly Gln Gln 235

Asn Gln Thr Ser Arg Lys Met Gln Val Tyr Leu Ser Ser Ser Asp Leu 245 250 Leu Thr Asn Ser Asn Thr Ile Leu Lys Gly Ala Glu Asp Asn Gly Val 265 Gly Phe Ile Leu Glu Ser Asn Gly Ser Pro Val Thr Leu Leu Asn Ile 275 280 Thr Asn Ser Ser Lys Gly Tyr Thr Asn Leu Lys Glu Val Ala Ala Lys 295 300 Ser Lys Leu Thr Asp Thr Thr Val Ser Ile Pro Ile Thr Ala Ser Tyr 310 315 320 Tyr Val Tyr Asp Thr Asn Lys Val Lys Ser Gly Ala Leu Glu Ala Thr 330 325 Ala Leu Ile Asn Val Lys Tyr Asp 340

<210> 309 <211> 826 <212> PRT <213> Escherichia coli

<400> 309

Met Leu Arg Met Thr Pro Leu Ala Ser Ala Ile Val Ala Leu Leu 10 Gly Ile Glu Ala Tyr Ala Ala Glu Glu Thr Phe Asp Thr His Phe Met 25 Ile Gly Gly Met Lys Asp Gln Gln Val Ala Asn Ile Arg Leu Asp Asp 35 40 Asn Gln Pro Leu Pro Gly Gln Tyr Asp Ile Asp Ile Tyr Val Asn Lys 55 Gln Trp Arg Gly Lys Tyr Glu Ile Ile Val Lys Asp Asn Pro Gln Glu 70 75 Thr Cys Leu Ser Arg Glu Val Ile Lys Arg Leu Gly Ile Asn Ser Asp 90 Asn Phe Ala Ser Gly Lys Gln Cys Leu Thr Phe Glu Gln Leu Val Gln 105 Gly Gly Ser Tyr Thr Trp Asp Ile Gly Val Phe Arg Leu Asp Phe Ser 120 Val Pro Gln Ala Trp Val Glu Glu Leu Glu Ser Gly Tyr Val Pro Pro 135 Glu Asn Trp Glu Arg Gly Ile Asn Ala Phe Tyr Thr Ser Tyr Tyr Leu 150 155 Ser Gln Tyr Tyr Ser Asp Tyr Lys Ala Ser Gly Asn Asn Lys Ser Thr 170 Tyr Val Arg Phe Asn Ser Gly Leu Asn Leu Leu Gly Trp Gln Leu His 180 185 190 Ser Asp Ala Ser Phe Ser Lys Thr Asn Asn Asn Pro Gly Val Trp Lys 195 200 205 Ser Asn Thr Leu Tyr Leu Glu Arg Gly Phe Ala Gln Leu Leu Gly Thr 215 220 Leu Arg Val Gly Asp Met Tyr Thr Ser Ser Asp Ile Phe Asp Ser Val 230 235 240 Arg Phe Arg Gly Val Arg Leu Phe Arg Asp Met Gln Met Leu Pro Asn 245 . 250 Ser Lys Gln Asn Phe Thr Pro Arg Val Gln Gly Ile Ala Gln Ser Asn 265 Ala Leu Val Thr Ile Glu Gln Asn Gly Phe Val Val Tyr Gln Lys Glu 280 285 Val Pro Pro Gly Pro Phe Ala Ile Thr Asp Leu Gln Leu Ala Gly Gly 295 300 Gly Ala Asp Leu Asp Val Ser Val Lys Glu Ala Asp Gly Ser Val Thr

305	_	_		_	310				_	315		_		_	320
	Tyr	,		325					330					335	_
	Ser		340					345					350		
Ser	Lys	Gln 355	Ser	Asp	Phe	Val	Gln 360	Ala	GLY	Tyr	Gln	Tyr 365	Gly	Phe	Asn
Asn	Leu 370	Leu	Thr	Leu	Tyr	Gly 375	Gly	Ser	Met	Val	Ala 380	Asn	Asn	Tyr	Tyr
Ala 385	Phe	Thr	Leu	Gly	Ala 390	Gly	Trp	Asn	Thr	Arg 395	Ile	Gly	Ala	Ile	Ser 400
Val	Asp	Ala	Thr	Lys 405	Ser	His	Ser	Lys	Gln 410	Asp	Asn	Gly	Asp	Val 415	Phe
Asp	Gly	Gln	Ser 420	Tyr	Gln	Ile	Ala	Tyr 425	Asn	Lys	Phe	Val	Ser 430	Gln	Thr
Ser	Thr	Arg 435	Phe	Gly	Leu	Ala	Ala 440	Trp	Arg	Tyr	Ser	Ser 445	Arg	Asp	Tyr
Arg	Thr 450	Phe	Asn	Asp	His	Val 455	Trp	Ala	Asn	Asn	Lys 460	Asp	Asn	Tyr	Arg
Arg 465	Asp	Glu	Asn	Asp	Val 470	Tyr	Asp	Ile	Ala	Asp 475	Tyr	Tyr	Gln	Asn	Asp 480
Phe	Gly	Arg	Lys	Asn 485	Ser	Phe	Ser	Ala	Asn 490	Met	Ser	Gln	Ser	Leu 495	Pro
	Gly		500					505					510	-	_
Gly	Arg	Ser 515	Gly	Ser	Ser	Lys	Asp 520	Tyr	Gln	Leu	Ser	Tyr 525	Ser	Asn	Asn
Leu	Arg 530	Arg	Ile	Ser	Tyr	Thr 535	Leu	Ala	Ala	Ser	Gln 540	Ala	Tyr	Asp	Glu
545	His				550	_				555					560
	Trp			565					570	_			_	575	
	Ser		580					585					590		
	Ser	595					600					605	_		
	Ser 610					615					620	_			
625	Trp	Asn	Ата	Pro	630	Ата	'l'nr	vaı	Asn	635	ser	Tyr	Ser	GIn	Ser 640
	Thr	Tyr	Arg	Gln 645		Gly	Ala	Ser	Val 650		Gly	Gly	Ile	Val 655	
Trp	Ser	Gly	Gly 660	Val	Asn	Leu	Ala	Asn 665	Arg	Leu	Ser	Glu	Thr 670		Ala
Val	Met	Asn 675	Ala	Pro	Gly	Ile	Lys 680	Asp	Ala	Tyr	Val	Asn 685	Gly	Gln	Lys
Tyr	Arg 690	Thr	Thr	Asn	Arg	Asn 695	Gly	Val	Val	Ile	Tyr 700	Asp	Gly	Met	Thr
705	Tyr				710				-	715				•	720
Glu	Ala	Glu	Leu	Arg 725	Gly	Asn	Arg	Lys	Ile 730	Ala	Ala	Pro	Tyr	Arg 735	Gly
	Val		740					745				_	750	_	
	Lys	755					760					765	•	_	
	Asn 770					775					780	_			
Gln 785	Leu	Phe	Ile	Arg	Thr 790	Asn	Glu	Val	Pro	Pro 795	Ser	Val	Asn	Val	Ala 800

PCT/US00/34419 WO 01/48209°

Ile Asp Lys Gln Gln Gly Leu Ser Cys Thr Ile Thr Phe Gly Lys Glu 805 810 Ile Asp Glu Ser Arg Asn Tyr Ile Cys Gln

<210> 310 <211> 239 <212> PRT

<213> Escherichia coli

<400> 310

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<210> 311 <211> 180 <212> PRT <213> Escherichia coli

<400> 311

Met Lys Arg Ser Ile Ile Ala Ala Val Phe Ser Ser Phe Phe Met 10 Ser Ala Gly Val Phe Ala Ala Asp Val Asp Thr Gly Thr Leu Thr Ile 20 25 Lys Gly Asn Ile Ala Glu Ser Pro Cys Lys Phe Glu Ala Gly Gly Asp Ser Val Ser Ile Asn Met Pro Thr Val Pro Thr Ser Val Phe Glu Gly 55 Lys Ala Lys Tyr Ser Thr Tyr Asp Asp Ala Val Gly Val Thr Ser Ser 70 Met Leu Lys Ile Ser Cys Pro Lys Glu Val Ala Gly Val Lys Leu Ser

<210> 312 <211> 95 <212> PRT <213> Escherichia coli

<400> 312

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 Leu His Arg
 Ser Pro Trp Leu Thr
 Asp Phe Ala Ala
 Ala 10
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<210> 313 <211> 119 <212> PRT <213> Escherichia coli

<400> 313

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115

<210> 314 <211> 128

<212> PRT <213> Escherichia coli

<400> 314 Met Arg Phe Ala Ile Val Val Thr Gly Pro Ala Tyr Gly Thr Gln Gln 10 Ala Ser Ser Ala Phe Gln Phe Ala Gln Ala Leu Ile Ala Asp Gly His Glu Leu Ser Ser Val Phe Phe Tyr Arg Glu Gly Val Tyr Asn Ala Asn . 40 Gln Leu Thr Ser Pro Ala Ser Asp Glu Phe Asp Leu Val Arg Ala Trp 55 Gln Gln Leu Asn Ala Gln His Gly Val Ala Leu Asn Ile Cys Val Ala 70 Ala Ala Leu Arg Arg Gly Val Val Asp Glu Thr Glu Ala Gly Arg Leu 90 Gly Leu Ala Ser Ser Asn Leu Gln Gln Gly Phe Thr Leu Ser Gly Leu 105 Gly Ala Leu Ala Glu Ala Ser Leu Thr Cys Asp Arg Val Val Gln Phe 120

<210> 315

<211> 244

<212> PRT

<213> Escherichia coli

<400> 315

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<210> 316 <211> 84 <212> PRT <213> Escherichia coli <400> 316 Met Thr Asp Lys Ile Arg Thr Leu Gln Gly Arg Val Val Ser Asp Lys 10 Met Glu Lys Ser Ile Val Val Ala Ile Glu Arg Phe Val Lys His Pro 25 Ile Tyr Gly Lys Phe Ile Lys Arg Thr Thr Lys Leu His Val His Asp 40 Glu Asn Asn Glu Cys Gly Ile Gly Asp Val Val Glu Ile Arg Glu Cys Arg Pro Leu Ser Lys Thr Lys Ser Trp Thr Leu Val Arg Val Val Glu Lys Ala Val Leu <210> 317 <211> 63 <212> PRT <213> Escherichia coli <400> 317 Met Lys Ala Lys Glu Leu Arg Glu Lys Ser Val Glu Glu Leu Asn Thr 10 Glu Leu Leu Asn Leu Leu Arg Glu Gln Phe Asn Leu Arg Met Gln Ala 25 Ala Ser Gly Gln Leu Gln Gln Ser His Leu Leu Lys Gln Val Arg Arg 40 Asp Val Ala Arg Val Lys Thr Leu Leu Asn Glu Lys Ala Gly Ala <210> 318 <211> 136 <212> PRT <213> Escherichia coli <400> 318 Met Leu Gln Pro Lys Arg Thr Lys Phe Arg Lys Met His Lys Gly Arg 10 Asn Arg Gly Leu Ala Gln Gly Thr Asp Val Ser Phe Gly Ser Phe Gly 25 Leu Lys Ala Val Gly Arg Gly Arg Leu Thr Ala Arg Gln Ile Glu Ala 40 Ala Arg Arg Ala Met Thr Arg Ala Val Lys Arg Gln Gly Lys Ile Trp 55 Ile Arg Val Phe Pro Asp Lys Pro Ile Thr Glu Lys Pro Leu Ala Val 75 Arg Met Gly Lys Gly Lys Gly Asn Val Glu Tyr Trp Val Ala Leu Ile 85 Gln Pro Gly Lys Val Leu Tyr Glu Met Asp Gly Val Pro Glu Glu Leu

100 105 110

Ala Arg Glu Ala Phe Lys Leu Ala Ala Lys Leu Pro Ile Lys Thr
115 120 125

135

Thr Phe Val Thr Lys Thr Val Met

<210> 319

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<211> 233
<212> PRT
<213> Escherichia coli
<400> 319
Met Gly Gln Lys Val His Pro Asn Gly Ile Arg Leu Gly Ile Val Lys
                                   10
Pro Trp Asn Ser Thr Trp Phe Ala Asn Thr Lys Glu Phe Ala Asp Asn
                               25
Leu Asp Ser Asp Phe Lys Val Arg Gln Tyr Leu Thr Lys Glu Leu Ala
                          40
Lys Ala Ser Val Ser Arg Ile Val Ile Glu Arg Pro Ala Lys Ser Ile
                       55
Arg Val Thr Ile His Thr Ala Arg Pro Gly Ile Val Ile Gly Lys Lys
                   70
Gly Glu Asp Val Glu Lys Leu Arg Lys Val Val Ala Asp Ile Ala Gly
               85
Val Pro Ala Gln Ile Asn Ile Ala Glu Val Arg Lys Pro Glu Leu Asp
                              105
Ala Lys Leu Val Ala Asp Ser Ile Thr Ser Gln Leu Glu Arg Arg Val
                          120
Met Phe Arg Arg Ala Met Lys Arg Ala Val Gln Asn Ala Met Arg Leu
                      135
Gly Ala Lys Gly Ile Lys Val Glu Val Ser Gly Arg Leu Gly Gly Ala
                  150
                                       155
Glu Ile Ala Arg Thr Glu Trp Tyr Arg Glu Gly Arg Val Pro Leu His
               165 '
                                   170
Thr Leu Arg Ala Asp Ile Asp Tyr Asn Thr Ser Glu Ala His Thr Thr
                              185
           180
Tyr Gly Val Ile Gly Val Lys Val Trp Ile Phe Lys Gly Glu Ile Leu
                          200
       195
Gly Gly Met Ala Ala Val Glu Gln Pro Glu Lys Pro Ala Ala Gln Pro
                      215
Lys Lys Gln Gln Arg Lys Gly Arg Lys
                   230
<210> 320 '
<211> 110
<212> PRT
<213> Escherichia coli
<400> 320
Met Glu Thr Ile Ala Lys His Arg His Ala Arg Ser Ser Ala Gln Lys
          5 10
Val Arg Leu Val Ala Asp Leu Ile Arg Gly Lys Lys Val Ser Gln Ala
                              25
Leu Asp Ile Leu Thr Tyr Thr Asn Lys Lys Ala Ala Val Leu Val Lys
                          40 -
Lys Val Leu Glu Ser Ala Ile Ala Asn Ala Glu His Asn Asp Gly Ala
                      55
Asp Ile Asp Asp Leu Lys Val Thr Lys Ile Phe Val Asp Glu Gly Pro
                  70
                                   75
Ser Met Lys Arg Ile Met Pro Arg Ala Lys Gly Arg Ala Asp Arg Ile
              85
                                 90
Leu Lys Arg Thr Ser His Ile Thr Val Val Val Ser Asp Arg
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110

·<210> 321 <211> 92 <212> PRT <213> Escherichia coli

<400> 321

Met Pro Arg Ser Leu Lys Lys Gly Pro Phe Ile Asp Leu His Leu Leu 10 Lys Lys Val Glu Lys Ala Val Glu Ser Gly Asp Lys Lys Pro Leu Arg 20 25 Thr Trp Ser Arg Arg Ser Thr Ile Phe Pro Asn Met Ile Gly Leu Thr 40 Ile Ala Val His Asn Gly Arg Gln His Val Pro Val Phe Val Thr Asp 60 55 Glu Met Val Gly His Lys Leu Gly Glu Phe Ala Pro Thr Arg Thr Tyr 70 Arg Gly His Ala Ala Asp Lys Lys Ala Lys Lys

<210> 322 <211> 273 <212> PRT <213> Escherichia coli

<400> 322

Met Ala Val Val Lys Cys Lys Pro Thr Ser Pro Gly Arg Arg His Val 10 Val Lys Val Val Asn Pro Glu Leu His Lys Gly Lys Pro Phe Ala Pro Leu Leu Glu Lys Asn Ser Lys Ser Gly Gly Arg Asn Asn Asn Gly Arg 40 Ile Thr Thr Arg His Ile Gly Gly His Lys Gln Ala Tyr Arg Ile Val Asp Phe Lys Arg Asn Lys Asp Gly Ile Pro Ala Val Val Glu Arg Leu Glu Tyr Asp Pro Asn Arg Ser Ala Asn Ile Ala Leu Val Leu Tyr 90 Lys Asp Gly Glu Arg Arg Tyr Ile Leu Ala Pro Lys Gly Leu Lys Ala 105 Gly Asp Gln Ile Gln Ser Gly Val Asp Ala Ala Ile Lys Pro Gly Asn 115 120 125 Thr Leu Pro Met Arg Asn Ile Pro Val Gly Ser Thr Val His Asn Val 135 140 Glu Met Lys Pro Gly Lys Gly Gly Gln Leu Ala Arg Ser Ala Gly Thr 150 155 Tyr Val Gln Ile Val Ala Arg Asp Gly Ala Tyr Val Thr Leu Arg Leu 165 .170 Arg Ser Gly Glu Met Arg Lys Val Glu Ala Asp Cys Arg Ala Thr Leu 185 Gly Glu Val Gly Asn Ala Glu His Met Leu Arg Val Leu Gly Lys Ala 200 Gly Ala Ala Arg Trp Arg Gly Val Arg Pro Thr Val Arg Gly Thr Ala 215 220 Met Asn Pro Val Asp His Pro His Gly Gly Glu Gly Arg Asn Phe 230 235 Gly Lys His Pro Val Thr Pro Trp Gly Val Gln Thr Lys Gly Lys Lys 250 245 Thr Arg Ser Asn Lys Arg Thr Asp Lys Phe Ile Val Arg Arg Arg Ser 260 265

Lys

<210> 323 <211> 100 <212> PRT <213> Escherichia coli <400> 323 Met Ile Arg Glu Glu Arg Leu Leu Lys Val Leu Arg Ala Pro His Val 10 Ser Glu Lys Ala Ser Thr Ala Met Glu Lys Ser Asn Thr Ile Val Leu 25 Lys Val Ala Lys Asp Ala Thr Lys Ala Glu Ile Lys Ala Ala Val Gln 40 Lys Leu Phe Glu Val Glu Val Glu Val Val Asn Thr Leu Val Val Lys Gly Lys Val Lys Arg His Gly Gln Arg Ile Gly Arg Arg Ser Asp Trp 70 75 Lys Lys Ala Tyr Val Thr Leu Lys Glu Gly Gln Asn Leu Asp Phe Val 85 Gly Gly Ala Glu 100 <210> 324 <211> 201 <212> PRT <213> Escherichia coli <400> 324 Met Glu Leu Val Leu Lys Asp Ala Gln Ser Ala Leu Thr Val Ser Glu 10 Thr Thr Phe Gly Arg Asp Phe Asn Glu Ala Leu Val His Gln Val Val 25 Val Ala Tyr Ala Ala Gly Ala Arg Gln Gly Thr Arg Ala Gln Lys Thr 40 Arg Ala Glu Val Thr Gly Ser Gly Lys Lys Pro Trp Arg Gln Lys Gly 55 Thr Gly Arg Ala Arg Ser Gly Ser Ile Lys Ser Pro Ile Trp Arg Ser 70 75 . 80 Gly Gly Val Thr Phe Ala Ala Arg Pro Gln Asp His Ser Gln Lys Val 85 90 Asn Lys Lys Met Tyr Arg Gly Ala Leu Lys Ser Ile Leu Ser Glu Leu 100 105 110 Val Arg Gln Asp Arg Leu Ile Val Val Glu Lys Phe Ser Val Glu Ala 115 120 125 Pro Lys Thr Lys Leu Leu Ala Gln Lys Leu Lys Asp Met Ala Leu Glu 135 140 Asp Val Leu Ile Ile Thr Gly Glu Leu Asp Glu Asn Leu Phe Leu Ala 155 150

Ala Arg Asn Leu His Lys Val Asp Val Arg Asp Ala Thr Gly Ile Asp

Pro Val Ser Leu Ile Ala Phe Asp Lys Val Val Met Thr Ala Asp Ala

185

165 170

180

Val Lys Gln Val Glu Glu Met Leu Ala

<210> 325

<211> 209 <212> PRT <213> Escherichia coli

<400> 325

Met Ile Gly Leu Val Gly Lys Lys Val Gly Met Thr Arg Ile Phe Thr 10 Glu Asp Gly Val Ser Ile Pro Val Thr Val Ile Glu Val Glu Ala Asn 20 25 Arg Val Thr Gln Val Lys Asp Leu Ala Asn Asp Gly Tyr Arg Ala Ile 40 45 Gln Val Thr Thr Gly Ala Lys Lys Ala Asn Arg Val Thr Lys Pro Glu 55 Ala Gly His Phe Ala Lys Ala Gly Val Glu Ala Gly Arg Gly Leu Trp 70 75 Glu Phe Arg Leu Ala Glu Glu Glu Glu Phe Thr Val Gly Gln Ser Ile 90 Ser Val Glu Leu Phe Ala Asp Val Lys Lys Val Asp Val Thr Gly Thr 105 110 Ser Lys Gly Lys Gly Phe Ala Gly Thr Val Lys Arg Trp Asn Phe Arg 120 Thr Gln Asp Ala Thr His Gly Asn Ser Leu Ser His Arg Val Pro Gly 135 140 Ser Ile Gly Gln Asn Gln Thr Pro Gly Lys Val Phe Lys Gly Lys Lys 155 150 Met Ala Gly Gln Met Gly Asn Glu Arg Val Thr Val Gln Ser Leu Asp 165 170 Val Val Arg Val Asp Ala Glu Arg Asn Leu Leu Val Lys Gly Ala 185 190 Val Pro Gly Ala Thr Gly Ser Asp Leu Ile Val Lys Pro Ala Val Lys 200 Ala

<210> 326 <211> 103 <212> PRT <213> Escherichia coli

<400> 326

Met Gln Asn Gln Arg Ile Arg Ile Arg Leu Lys Ala Phe Asp His Arg 1 , 5 10 Leu Ile Asp Gln Ala Thr Ala Glu Ile Val Glu Thr Ala Lys Arg Thr 20 25 Gly Ala Gln Val Arg Gly Pro Ile Pro Leu Pro Thr Arg Lys Glu Arg 40 Phe Thr Val Leu Ile Ser Pro His Val Asn Lys Asp Ala Arg Asp Gln 55 Tyr Glu Ile Arg Thr His Leu Arg Leu Val Asp Ile Val Glu Pro Thr 70 75 Glu Lys Thr Val Asp Ala Leu Met Arg Leu Asp Leu Ala Ala Gly Val 90 85 Asp Val Gln Ile Ser Leu Gly 100 .

<210> 327 <211> 104 <212> PRT <213> Escherichia coli

<400> 327 Met Ile Arg Lys Ala Phe Val Met Gln Val Asn Pro Asp Ala His Glu 10 Glu Tyr Gln Arg Arg His Asn Pro Ile Trp Pro Glu Leu Glu Ala Val Leu Lys Ser His Gly Ala His Asn Tyr Ala Ile Tyr Leu Asp Lys Ala 40 Arg Asn Leu Leu Phe Ala Met Val Glu Ile Glu Ser Glu Glu Arg Trp 55 Asn Ala Val Ala Ser Thr Asp Val Cys Gln Arg Trp Trp Lys Tyr Met 70 Thr Asp Val Met Pro Ala Asn Pro Asp Asn Ser Pro Val Ser Ser Glu 85 90 Leu Gln Glu Val Phe Tyr Leu Pro 100

<210> 328 <211> 287 <212> PRT <213> Escherichia coli

<400> 328

Met Ile Arg Ser Met Thr Ala Tyr Ala Arg Arg Glu Ile Lys Gly Glu 10 Trp Gly Ser Ala Thr Trp Glu Met Arg Ser Val Asn Gln Arg Tyr Leu 25 Glu Thr Tyr Phe Arg Leu Pro Glu Gln Phe Arg Ser Leu Glu Pro Val 40 Val Arg Glu Arg Ile Arg Ser Arg Leu Thr Arg Gly Lys Val Glu Cys 55 60 Thr Leu Arg Tyr Glu Pro Asp Val Ser Ala Gln Gly Glu Leu Ile Leu 75 70 Asn Glu Lys Leu Ala Lys Gln Leu Val Thr Ala Ala Asn Trp Val Lys 90 Met Gln Ser Asp Glu Gly Glu Ile Asn Pro Val Asp Ile Leu Arg Trp 105 Pro Gly Val Met Ala Ala Gln Glu Gln Asp Leu Asp Ala Ile Ala Ala 120 Glu Ile Leu Ala Ala Leu Asp Gly Thr Leu Asp Asp Phe Ile Val Ala 140 135 Arg Glu Thr Glu Gly Gln Ala Leu Lys Ala Leu Ile Glu Gln Arg Leu 150 155 160 Glu Gly Val Thr Ala Glu Val Val Lys Val Arg Ser His Met Pro Glu 170 Ile Leu Gln Trp Gln Arg Glu Arg Leu Val Ala Lys Leu Glu Asp Ala 180 185 Gln Val Gln Leu Glu Asn Asn Arg Leu Glu Gln Glu Leu Val Leu Leu . 200 Ala Gln Arg Ile Asp Val Ala Glu Glu Leu Asp Arg Leu Glu Ala His 215 220 Val Lys Glu Thr Tyr Asn Ile Leu Lys Lys Lys Glu Ala Val Gly Arg 230 235 Arg Leu Asp Phe Met Met Gln Glu Phe Asn Arg Glu Ser Asn Thr Leu 250 Ala Ser Lys Ser Ile Asn Ala Glu Val Thr Asn Ser Ala Ile Glu Leu Lys Val Leu Ile Glu Gln Met Arg Glu Gln Ile Gln Asn Ile Glu 280

<210> 329 <211> 163 <212> PRT <213> Escherichia coli

<400> 329

Met Ser Thr Glu Thr Ile Glu Ile Phe Asn Asn Ser Asp Glu Trp Ala 10 Asn Gln Leu Lys His Ala Leu Ser Lys Gly Glu Asn Leu Ala Leu Leu 20 25 His Gly Leu Thr Pro Asp Ile Leu Asp Arg Ile Tyr Ala Tyr Ala Phe 40 Asp Tyr His Glu Lys Gly Asn Ile Thr Asp Ala Glu Ile Tyr Tyr Lys 55 Phe Leu Cys Ile Tyr Ala Phe Glu Asn His Glu Tyr Leu Lys Asp Phe 70 75 Ala Ser Val Cys Gln Pro Lys Lys Lys Tyr Gln Gln Ala Tyr Asp Leu 90 Tyr Lys Leu Ser Tyr Asn Tyr Phe Pro Tyr Asp Asp Tyr Ser Val Ile 105 Tyr Arg Met Gly Gln Cys Gln Ile Gly Ala Lys Asn Ile Asp Asn Ala 120 Met Gln Cys Phe Tyr His Ile Ile Asn Asn Cys Glu Asp Asp Ser Val 135 140 Lys Ser Lys Ala Gln Ala Tyr Ile Glu Leu Leu Asn Asp Asn Ser Glu 150 155 Asp Asn Gly

<210> 330 <211> 648 <212> PRT <213> Escherichia coli

<400> 330

Met Asn Ile Leu Gly Phe Phe Gln Arg Leu Gly Arg Ala Leu Gln Leu Pro Ile Ala Val Leu Pro Val Ala Ala Leu Leu Leu Arg Phe Gly Gln Pro Asp Leu Leu Asn Val Ala Phe Ile Ala Gln Ala Gly Gly Ala Ile 40 Phe Asp Asn Leu Ala Leu Ile Phe Ala Ile Gly Val Ala Ser Ser Trp 55 Ser Lys Asp Ser Ala Gly Ala Ala Ala Leu Ala Gly Ala Val Gly Tyr 70 75 Phe Val Leu Thr Lys Ala Met Val Thr Ile Asn Pro Glu Ile Asn Met 90 85 Gly Val Leu Ala Gly Ile Ile Thr Gly Leu Val Gly Gly Ala Ala Tyr 105 Asn Arg Trp Ser Asp Ile Lys Leu Pro Asp Phe Leu Ser Phe Phe Gly 115 120 125 Gly Lys Arg Phe Val Pro Ile Ala Thr Gly Phe Phe Cys Leu Val Leu 135 140 Ala Ala Ile Phe Gly Tyr Val Trp Pro Pro Val Gln His Ala Ile His 150 155 Ala Gly Gly Glu Trp Ile Val Ser Ala Gly Ala Leu Gly Ser Gly Ile 165 170 Phe Gly Phe Ile Asn Arg Leu Leu Ile Pro Thr Gly Leu His Gln Val 185

Leu Asn	Thr 195	Ile	Ala	Trp	Phe	Gln 200	Ile	Gly	Glu	Phe	Thr 205	Asn	Ala	Ala
Gly Thr 210	Val	Phe	His	Gly	Asp 215	Ile	Asn	Arg	Phe	Tyr 220	Ala	Gly	qeA	Gly
Thr Ala 225	Gly	Met	Phe	Met 230	Ser	Gly	Phe	Phe	Pro 235	Ile	Met	Met	Phe	Gly 240
Leu Pro	Gly	Ala	Ala 245	Leu	Ala	Met	Tyr	Phe 250	Ala	Ala	Pro	Lys	Glu 255	Arg
Arg Pro	Met	Val 260	Gly	Gly	Met	Leu	Leu 265	Ser	Val	Ala	Val	Thr 270	Ala	Phe
Leu Thr	Gly 275	Val	Thr	Glu	Pro	Leu 280	Glu	Phe	Leu	Phe	Met 285	Phe	Leu	Ala
Pro Leu 290	Leu	Tyr	Leu	Leu	His 295	Ala	Leu	Leu	Thr	Gly 300	Ile	Ser	Leu	Phe
Val Ala 305	Thr	Leu	Leu	Gly 310	Ile	His	Ala	Gly ·	Phe 315	Ser	Phe	Ser	Ala	Gly 320
Ala Ile	_		325					330					335	
Val Trp		340				_	345					350	_	
Val Val	355					360					365.			_
Arg Glu 370	_	_			375					380				
Thr Glu		_		390					395	_				400
Gly Gly		_	405					410					415	
Arg Leu		420					425					430	_	_
Arg Leu	435			_		440					445			
Val Ile 450					455					460				
Val Val 465				470					475					480
Ala Thr			485					490					495	
Ser Ile Asp Gln		500					505					510		
_	515		-			520			-		525	_		_
Val Ala 530 Thr Ile				•	535					540				
545 Glu Lys				550					555			-	:	560·
			565					570					575	
Leu Glu Ser Ala		580					585					590		
Asn Ala	595					600					605			
610 Phe Ser	_				615				_	620				
625				630			GTII	GTÀ	635	TT6	val	ara	GTĀ	640
Thr Pro	TIEU	TÅT	645		пåя	nys								

<210> 331

<211> 412 <212> PRT <213> Escherichia coli

<400> 331 Met Lys Thr Ile Phe Arg Tyr Ile Leu Phe Leu Ala Leu Tyr Ser Cys 10 Cys Asn Thr Val Ser Ala Tyr Thr Ser Phe Ile Val Gly Asn Asn Ala 20 25 Gly Val Asp Asn Tyr Arg Gly Pro Ser Thr Ala Ala Gln Met Thr Phe 40 Asn Tyr Thr Ser Thr Ala Ser Asn Leu Val Phe Tyr Lys Pro Thr Gln 55 60 Leu Gly Pro Thr Gly Val Lys Met Tyr Trp Ser Tyr Leu Asp Thr Gly 70 75 Thr Gly Gly Gly Ile Leu Tyr Cys Asn Thr Ser Gly Arg Ala Asn Pro 85 90 Gly Pro Ile Thr Ile Glu Asn Ala Met Val Tyr Ser Gly Lys Asp Tyr 105 Gly His Lys Leu Phe Asn Thr Ser Val Pro Gly Leu Tyr Tyr Thr 120 Met Leu Ile Ser Arg Val Trp Ser Ala Tyr Asp Thr Ile Thr Asp Ile 135 Gln Ser Pro Gly Ile Tyr Ile Gly Asp Pro Ser Asn Gln Glu Phe Phe 150 155 Phe Ser Val Thr Asp Ser Asp Leu Gln Thr Lys Gly Cys Asn Lys Ala 165 170 Asp Asp Tyr Asp Lys Phe Trp Ala Ile Gly Gly Ile Val His Asn Ile 180 185 190 Thr Val Glu Phe Tyr Thr Asp Thr Asn Phe Asp Pro Thr Leu Asn Gln 200 Gln Val Gln Leu Ser Ser Ser Asn Tyr Leu Tyr Ser Phe Lys Ala 210 215 220 Tyr Ser Pro Gly Thr Lys Val Val Asp His Ser Asn His Ile Tyr Val 230 235 Asn Phe Thr Leu Asn Asn Val Lys Leu Thr Leu Pro Thr Cys Phe Thr 250 Ser Ile Leu Thr Gly Pro Ser Val Asn Gly Ser Thr Val Arg Met Gly 265 Glu Tyr Ser Ser Gly Thr Ile Lys Asn Gly Ala Ser Pro Val Pro Phe 280 Asp Ile Ser Leu Gln Asn Cys Ile Arg Val Arg Asn Ile Glu Thr Lys 295 300 Leu Val Thr Gly Lys Val Gly Thr Gln Asn Thr Gln Leu Leu Gly Asn 315 310 Thr Leu Thr Gly Ser Thr Ala Ala Lys Gly Val Gly Val Leu Ile Glu 325 330 Gly Leu Ala Thr Ser Lys Asn Pro Leu Met Thr Leu Lys Pro Asn Asp 340 345 Thr Asn Ser Val Tyr Ile Asp Tyr Glu Thr Glu Asp Asp Thr Ser Asp 360 Gly Val Tyr Pro Asn Gln Gly Asn Gly Thr Ser Gln Pro Leu His Phe 375 380 Gln Ala Thr Leu Lys Gln Asp Gly Asn Ile Ala Ile Glu Pro Gly Glu 390 395 Phe Lys Ala Thr Ser Thr Phe Gln Val Thr Tyr Pro

<210> 332 <211> 198

<212> PRT

<213> Escherichia coli

<400> 332

Met His Pro Thr Gln Arg Lys Leu Met Lys Arg Ile Ile Leu Phe Leu Ser Leu Leu Phe Cys Ile Ala Cys Pro Ala Ile Ala Gly Gln Asp Ile 25 Asp Leu Val Ala Asn Val Lys Asn Ser Thr Cys Lys Ser Gly Ile Ser Asn Gln Gly Asn Ile Asp Leu Gly Val Val Gly Val Gly Tyr Phe Ser Gly Asn Val Thr Pro Glu Ser Tyr Gln Pro Gly Gly Lys Glu Phe Thr 70 Ile Thr Val Ser Asp Cys Ala Leu Gln Gly Thr Gly Asp Val Leu Asn 90 Gln Leu His Ile Asp Phe Arg Ala Leu Ser Gly Val Met Ala Ala Gly 105 Ser Arg Gln Ile Phe Ala Asn Glu Ile Ser Ser Gly Ala Ser Asn Val 120 Gly Val Val Ile Phe Ser Thr Gln Asp Ser Ala Asn Thr Phe Asn Val 135 Leu Asn Ala Ser Gly Gly Ser Arg Ser Val Tyr Pro Val Met Ser Asp 150 155 Asp Met Asn Gly Ser Ser Trp Lys Phe Ser Thr Arg Met Gln Lys Ile 170 Asp Pro Ala Leu Ser Val Thr Ser Gly Gln Leu Met Ser His Val Leu 185 Val Asp Ile Tyr Tyr Glu 195

<210> 333

<211> 201

<212> PRT

<213> Escherichia coli

<400> 333

Met Met Thr Phe Lys Asn Leu Arg Tyr Gly Leu Ser Ser Ser Val Val 10 Leu Ala Ala Ser Leu Phe Ser Val Leu Ser Tyr Ala Ala Thr Asp Ser 20 25 Ile Gly Leu Thr Val Ile Thr Thr Val Glu Met Gly Thr Cys Thr Ala 40 Thr Leu Val Asn Asp Ser Asp Gln Asp Ile Ser Val Val Asp Phe Gly 55 Asp Val Tyr Ile Ser Glu Ile Asn Ala Lys Thr Lys Val Lys Thr Phe · 75 Lys Leu Lys Phe Lys Asp Cys Ala Gly Ile Pro Asn Lys Lys Ala Gln 90 Ile Lys Leu Thr Lys Arg Ala Thr Cys Glu Gly Thr Ala Asn Asp Gly 105 Ala Gly Phe Ala Asn Gly Ser Thr Ala Ala Asp Lys Ala Ser Ala Val 120 Ala Val Glu Val Trp Ser Thr Val Thr Pro Ala Thr Gly Ser Ala Thr 135 140 Gln Phe Ser Cys Val Thr Pro Ala Ser Gln Glu Val Thr Ile Ser Thr 150 155 Ala Ala Asn Ala Val Val Tyr Tyr Pro Met Ser Ala Arg Leu Val Val 170 Glu Lys Asn Lys Thr Val Asn Asn Val Thr Ala Gly Lys Phe Ser Ala

180 185 190
Pro Ala Thr Phe Thr Val Thr Tyr Asn
195 200

<210> 334 <211> 203

<212> PRT

<213> Escherichia coli

<400> 334

Met Glu Phe Gly Val Arg Phe Ser Asn Tyr Lys Gly Arg Gln Met Ile Lys Thr Thr Pro His Lys Ile Val Ile Leu Met Gly Ile Leu Leu Ser 20 25 Pro Ser Val Phe Ala Thr Asp Ile Asn Val Glu Phe Thr Ala Thr Val 40 Lys Ala Thr Thr Cys Asn Ile Thr Leu Thr Gly Asn Asn Val Thr Asn Asp Gly Asn Asn Asn Tyr Thr Leu Arg Ile Pro Lys Met Gly Leu Asp 70 75 Lys Ile Ala Asn Lys Thr Thr Glu Ser Gln Ala Asp Phe Lys Leu Val 90 Ala Ser Gly Cys Ser Ser Gly Ile Ser Trp Ile Asp Thr Thr Leu Thr 100 105 Gly Asn Ala Ser Ser Ser Pro Lys Leu Ile Ile Pro Gln Ser Gly 120 Asp Ser Ser Ser Thr Thr Ser Asn Ile Gly Met Gly Phe Lys Lys Arg 135 140 Thr Thr Asp Asp Ala Thr Phe Leu Lys Pro Asn Ser Ala Glu Lys Ile 150 155 Arg Trp Ser Thr Asp Glu Met Gln Pro Asp Lys Gly Leu Glu Met Thr 170 165 Val Ala Leu Arg Glu Thr Asp Ala Gly Gln Gly Val Pro Gly Asn Phe 185 Arg Ala Leu Ala Thr Phe Asn Phe Ile Tyr Gln

<210> 335 <211> 139

<212> PRT

<213> Escherichia coli

<400> 335

Met Ala Met Thr Tyr His Leu Asp Val Val Ser Ala Glu Gln Gln Met 10 Phe Ser Gly Leu Val Glu Lys Ile Gln Val Thr Gly Ser Glu Gly Glu 25 Leu Gly Ile Tyr Pro Gly His Ala Pro Leu Leu Thr Ala Ile Lys Pro 40 Gly Met Ile Arg Ile Val Lys Gln His Gly His Glu Glu Phe Ile Tyr 55 Leu Ser Gly Gly Ile Leu Glu Val Gln Pro Gly Asn Val Thr Val Leu 75 70 Ala Asp Thr Ala Ile Arg Gly Gln Asp Leu Asp Glu Ala Arg Ala Met 90 Glu Ala Lys Arg Lys Ala Glu Glu His Ile Ser Ser His Gly Asp 105 Val Asp Tyr Ala Gln Ala Ser Ala Glu Leu Ala Lys Ala Ile Ala Gln 115 120

Leu Arg Val Ile Glu Leu Thr Lys Lys Ala Met 130 135

<210> 336 <211> 460 <212> PRT <213> Escherichia coli

<400> 336

Met Ala Thr Gly Lys Ile Val Gln Val Ile Gly Ala Val Val Asp Val Glu Phe Pro Gln Asp Ala Val Pro Arg Val Tyr Asp Ala Leu Glu Val 25 Gln Asn Gly Asn Glu Arg Leu Val Leu Glu Val Gln Gln Gln Leu Gly 40 Gly Gly Ile Val Arg Thr Ile Ala Met Gly Ser Ser Asp Gly Leu Arg 55 60 Arg Gly Leu Asp Val Lys Asp Leu Glu His Pro Ile Glu Val Pro Val 70 75 Gly Lys Ala Thr Leu Gly Arg Ile Met Asn Val Leu Gly Glu Pro Val 90 85 Asp Met Lys Gly Glu Ile Gly Glu Glu Glu Arg Trp Ala Ile His Arg 105 100 Ala Ala Pro Ser Tyr Glu Glu Leu Ser Asn Ser Gln Glu Leu Leu Glu 120 125 Thr Gly Ile Lys Val Ile Asp Leu Met Cys Pro Phe Ala Lys Gly Gly 135 140 Lys Val Gly Leu Phe Gly Gly Ala Gly Val Gly Lys Thr Val Asn Met 150 155 Met Glu Leu Ile Arg Asn Ile Ala Ile Glu His Ser Gly Tyr Ser Val 170 Phe Ala Gly Val Gly Glu Arg Thr Arg Glu Gly Asn Asp Phe Tyr His 185 Glu Met Thr Asp Ser Asn Val Ile Asp Lys Val Ser Leu Val Tyr Gly 200 205 Gln Met Asn Glu Pro Pro Gly Asn Arg Leu Arg Val Ala Leu Thr Gly 215 220 Leu Thr Met Ala Glu Lys Phe Arg Asp Glu Gly Arg Asp Val Leu Leu 230 235 Phe Val Asp Asn Ile Tyr Arg Tyr Thr Leu Ala Gly Thr Glu Val Ser 245 250 Ala Leu Leu Gly Arg Met Pro Ser Ala Val Gly Tyr Gln Pro Thr Leu 260 265 Ala Glu Glu Met Gly Val Leu Gln Glu Arg Ile Thr Ser Thr Lys Thr 275 280 Gly Ser Ile Thr Ser Val Gln Ala Val Tyr Val Pro Ala Asp Asp Leu 300 295 Thr Asp Pro Ser Pro Ala Thr Thr Phe Ala His Leu Asp Ala Thr Val 310 315 Val Leu Ser Arg Gln Ile Ala Ser Leu Gly Ile Tyr Pro Ala Val Asp 325 330 Pro Leu Asp Ser Thr Ser Arg Gln Leu Asp Pro Leu Val Val Gly Gln 345 Glu His Tyr Asp Thr Ala Arg Gly Val Gln Ser Ile Leu Gln Arg Tyr 360 Gln Glu Leu Lys Asp Ile Ile Ala Ile Leu Gly Met Asp Glu Leu Ser 375 380 Glu Glu Asp Lys Leu Val Val Ala Arg Ala Arg Lys Ile Gln Arg Phe 390 395 Leu Ser Gln Pro Phe Phe Val Ala Glu Val Phe Thr Gly Ser Pro Gly

<210> 337 <211> 287 <212> PRT <213> Escherichia coli

<400> 337

Met Ala Gly Ala Lys Glu Ile Arg Ser Lys Ile Ala Ser Val Gln Asn Thr Gln Lys Ile Thr Lys Ala Met Glu Met Val Ala Ala Ser Lys Met 25 Arg Lys Ser Gln Asp Arg Met Ala Ala Ser Arg Pro Tyr Ala Glu Thr 40 Met Arg Lys Val Ile Gly His Leu Ala His Gly Asn Leu Glu Tyr Lys 55 His Pro Tyr Leu Glu Asp Arg Asp Val Lys Arg Val Gly Tyr Leu Val Val Ser Thr Asp Arg Gly Leu Cys Gly Gly Leu Asn Ile Asn Leu Phe 90 Lys Lys Leu Leu Ala Glu Met Lys Thr Trp Thr Asp Lys Gly Val Gln 105 Cys Asp Leu Ala Met Ile Gly Ser Lys Gly Val Ser Phe Phe Asn Ser 120 Val Gly Gly Asn Val Val Ala Gln Val Thr Gly Met Gly Asp Asn Pro 135 140 Ser Leu Ser Glu Leu Ile Gly Pro Val Lys Val Met Leu Gln Ala Tyr 155 Asp Glu Gly Arg Leu Asp Lys Leu Tyr Ile Val Ser Asn Lys Phe Ile 165 · 170 Asn Thr Met Ser Gln Val Pro Thr Ile Ser Gln Leu Pro Leu Pro 180 185 Ala Ser Asp Asp Asp Leu Lys His Lys Ser Trp Asp Tyr Leu Tyr 200 Glu Pro Asp Pro Lys Ala Leu Leu Asp Thr Leu Leu Arg Arg Tyr Val 215 220 Glu Ser Gln Val Tyr Gln Gly Val Val Glu Asn Leu Ala Ser Glu Gln 230 235 240 Ala Ala Arg Met Val Ala Met Lys Ala Ala Thr Asp Asn Gly Gly Ser 250 245 Leu Ile Lys Glu Leu Gln Leu Val Tyr Asn Lys Ala Arg Gln Ala Ser 265 Ile Thr Glu Leu Thr Glu Ile Val Ser Gly Ala Ala Ala Val 280

<210> 338 <211> 513 <212> PRT <213> Escherichia coli

<400> 338

Met Gln Leu Asn Ser Thr Glu Ile Ser Glu Leu Ile Lys Gln Arg Ile 1 5 10 15

Ala Gln Phe Asn Val Val Ser Glu Ala His Asn Glu Gly Thr Ile Val 20 25 Ser Val Ser Asp Gly Val Ile Arg Ile His Gly Leu Ala Asp Cys Met 40 Gln Gly Glu Met Ile Ser Leu Pro Gly Asn Arg Tyr Ala Ile Ala Leu 55 Asn Leu Glu Arg Asp Ser Val Gly Ala Val Val Met Gly Pro Tyr Ala 70 75 Asp Leu Ala Glu Gly Met Lys Val Lys Cys Thr Gly Arg Ile Leu Glu 90 85 Val Pro Val Gly Arg Gly Leu Leu Gly Arg Val Val Asn Thr Leu Gly 105 Ala Pro Ile Asp Gly Lys Gly Pro Leu Asp His Asp Gly Phe Ser Ala 120 Val Glu Ala Ile Ala Pro Gly Val Ile Glu Arg Gln Ser Val Asp Gln 135 140 Pro Val Gln Thr Gly Tyr Lys Ala Val Asp Ser Met Ile Pro Ile Gly 150 155 Arg Gly Gln Arg Glu Leu Ile Ile Gly Asp Arg Gln Thr Gly Lys Thr 170 165 Ala Leu Ala Ile Asp Ala Ile Ile Asn Gln Arg Asp Ser Gly Ile Lys 180 185 190 Cys Ile Tyr Val Ala Ile Gly Gln Lys Ala Ser Thr Ile Ser Asn Val 200 . 205 Val Arg Lys Leu Glu Glu His Gly Ala Leu Ala Asn Thr Ile Val Val 215 220 Val Ala Thr Ala Ser Glu Ser Ala Ala Leu Gln Tyr Leu Ala Pro Tyr 235 230 Ala Gly Cys Ala Met Gly Glu Tyr Phe Arg Asp Arg Gly Glu Asp Ala 250 245 Leu Ile Ile Tyr Asp Asp Leu Ser Lys Gln Ala Val Ala Tyr Arg Gln 260 . 265 Ile Ser Leu Leu Leu Arg Arg Pro Pro Gly Arg Glu Ala Phe Pro Gly 280 Asp Val Phe Tyr Leu His Ser Arg Leu Leu Glu Arg Ala Ala Arg Val 295 Asn Ala Glu Tyr Val Glu Ala Phe Thr Lys Gly Glu Val Lys Gly Lys 310 315 Thr Gly Ser Leu Thr Ala Leu Pro Ile Ile Glu Thr Gln Ala Gly Asp 330 Val Ser Ala Phe Val Pro Thr Asn Val Ile Ser Ile Thr Asp Gly Gln 345 Ile Phe Leu Glu Thr Asn Leu Phe Asn Ala Gly Ile Arg Pro Ala Val 360 Asn Pro Gly Ile Ser Val Ser Arg Val Gly Gly Ala Ala Gln Thr Lys 375 380 Ile Met Lys Lys Leu Ser Gly Gly Ile Arg Thr Ala Leu Ala Gln Tyr 390 395 Arg Glu Leu Ala Ala Phe Ser Gln Phe Ala Ser Asp Leu Asp Asp Ala 410 405 Thr Arg Lys Gln Leu Asp His Gly Gln Lys Val Thr Glu Leu Leu Lys 425 Gln Lys Gln Tyr Ala Pro Met Ser Val Ala Gln Gln Ser Leu Val Leu 440 Phe Ala Ala Glu Arg Gly Tyr Leu Ala Asp Val Glu Leu Ser Lys Ile 455 460 Gly Ser Phe Glu Ala Ala Leu Leu Ala Tyr Val Asp Arg Asp His Ala 470 475 Pro Leu Met Gln Glu Ile Asn Gln Thr Gly Gly Tyr Asn Asp Glu Ile 485 . 490 · Glu Gly Lys Leu Lys Gly Ile Leu Asp Ser Phe Lys Ala Thr Gln Ser

500 505 510

Trp

<210> 339

<211> 177

<212> PRT

<213> Escherichia coli

<400> 339

Met Ser Glu Phe Ile Thr Val Ala Arg Pro Tyr Ala Lys Ala Ala Phe 10 Asp Phe Ala Val Glu His Gln Ser Val Glu Arg Trp Gln Asp Met Leu 25 Ala Phe Ala Ala Glu Val Thr Lys Asn Glu Gln Met Ala Glu Leu Leu 40 Ser Gly Ala Leu Ala Pro Glu Thr Leu Ala Glu Ser Phe Ile Ala Val Cys Gly Glu Gln Leu Asp Glu Asn Gly Gln Asn Leu Ile Arg Val Met Ala Glu Asn Gly Arg Leu Asn Ala Leu Pro Asp Val Leu Glu Gln Phe 90 Ile His Leu Arg Ala Val Ser Glu Ala Thr Ala Glu Val Asp Val Ile 105 Ser Ala Ala Ala Leu Ser Glu Gln Gln Leu Ala Lys Ile Ser Ala Ala 120 Met Glu Lys Arg Leu Ser Arg Lys Val Lys Leu Asn Cys Lys Ile Asp 135 Lys Ser Val Met Ala Gly Val Ile Ile Arg Ala Gly Asp Met Val Ile 150 155 Asp Gly Ser Val Arg Gly Arg Leu Glu Arg Leu Ala Asp Val Leu Gln

Ser

<210> 340

<211> 156

<212> PRT

<213> Escherichia coli

<400> 340

Met Asn Leu Asn Ala Thr Ile Leu Gly Gln Ala Ile Ala Phe Val Leu 10 Phe Val Leu Phe Cys Met Lys Tyr Val Trp Pro Pro Leu Met Ala Ala 25 Ile Glu Lys Arg Gln Lys Glu Ile Ala Asp Gly Leu Ala Ser Ala Glu 40 Arg Ala His Lys Asp Leu Asp Leu Ala Lys Ala Ser Ala Thr Asp Gln 55 Leu Lys Lys Ala Lys Ala Glu Ala Gln Val Ile Ile Glu Gln Ala Asn 70 Lys Arg Arg Ser Gln Ile Leu Asp Glu Ala Lys Ala Glu Ala Glu Gln 90 Glu Arg Thr Lys Ile Val Ala Gln Ala Gln Ala Glu Ile Glu Ala Glu 105 Arg Lys Arg Ala Arg Glu Glu Leu Arg Lys Gln Val Ala Ile Leu Ala 120 Val Ala Gly Ala Glu Lys Ile Ile Glu Arg Ser Val Asp Glu Ala Ala

Asn Ser Asp Ile Val Asp Lys Leu Val Ala Glu Leu
145 150 155

<210> 341

<211> 79

<212> PRT

<213> Escherichia coli

<400> 341

Met Glu Asn Leu Asn Met Asp Leu Leu Tyr Met Ala Ala Ala Val Met

1 5 10 15

Met Gly Leu Ala Ala Ile Gly Ala Ala Ile Gly Ile Gly Ile Leu Gly

20 25 30

Cly Lys Pho Leu Gly Gly Ala Ala Arg Gly Pro Asp Leu Ile Pro Leu

Gly Lys Phe Leu Glu Gly Ala Ala Arg Gln Pro Asp Leu Ile Pro Leu 35 40 45

Leu Arg Thr Gln Phe Phe Ile Val Met Gly Leu Val Asp Ala Ile Pro 50 55 60

Met Ile Ala Val Gly Leu Gly Leu Tyr Val Met Phe Ala Val Ala 65 70 75

<210> 342

<211> 271

<212> PRT

<213> Escherichia coli

<400> 342

 Met Ala Ser Glu Asn Met Thr Pro Gln Asp Tyr Ile Gly His Leu

 1
 5
 10
 15
 15

 Asn Asn Leu Gln Leu Asp Leu Asp Leu Arg Thr Phe Ser Leu Val Asp Pro Gln 20
 25
 30

 Asn Pro Pro Ala Thr Phe Trp Thr Ile Asn Ile Asp Ser Met Phe Phe 35
 40
 45

 Ser Val Val Leu Gly Leu Leu Phe Leu Val Leu Phe Arg Ser Val Ala 50
 55
 60

 Lys Lys Ala Thr Ser Gly Val Pro Gly Lys Phe Gln Thr Ala Ile Glu

65 70 75 80
Leu Val Ile Gly Phe Val Asn Gly Ser Val Lys Asp Met Tyr His Gly
85 90 95

Lys Ser Lys Leu Ile Ala Pro Leu Ala Leu Thr Ile Phe Val Trp Val

Phe Leu Met Asn Leu Met Asp Leu Leu Pro Ile Asp Leu Leu Pro Tyr
115 120 125

Ile Ala Glu His Val Leu Gly Leu Pro Ala Leu Arg Val Val Pro Ser 130 135 140

Ala Asp Val Asn Val Thr Leu Ser Met Ala Leu Gly Val Phe Ile Leu 145 150 155 160

Ile Leu Phe Tyr Ser Ile Lys Met Lys Gly Ile Gly Gly Phe Thr Lys
165 170 175

Glu Leu Thr Leu Gln Pro Phe Asn His Trp Ala Phe Ile Pro Val Asn 180 185 190

Leu Ile Leu Glu Gly Val Ser Leu Leu Ser Lys Pro Val Ser Leu Gly
195 200 205

Leu Arg Leu Phe Gly Asn Met Tyr Ala Gly Glu Leu Ile Phe Ile Leu 210 215 220

Ile Ala Gly Leu Leu Pro Trp Trp Ser Gln Trp Ile Leu Asn Val Pro 225 230 235 . 240

Trp Ala Ile Phe His Ile Leu Ile Ile Thr Leu Gln Ala Phe Ile Phe 245 250 255

Met Val Leu Thr Ile Val Tyr Leu Ser Met Ala Ser Glu Glu His

260 265 270

<210> 343

<211> 130

<212> PRT

<213> Escherichia coli

<400> 343

Met Lys Asn Val Met Ser Val Ser Leu Val Ser Arg Asn Val Ala Arg 5 10 Lys Leu Leu Val Gln Leu Leu Val Val Ile Ala Ser Gly Leu Leu 25 Phe Ser Leu Lys Asp Pro Phe Trp Gly Val Ser Ala Ile Ser Gly Gly 40 Leu Ala Val Phe Leu Pro Asn Val Leu Phe Met Ile Phe Ala Trp Arg 55 His Gln Ala His Thr Pro Ala Lys Gly Arg Val Ala Trp Thr Phe Ala 70 75 Phe Gly Glu Ala Phe Lys Val Leu Ala Met Leu Val Leu Val Val 90 Ala Leu Ala Val Leu Lys Ala Val Phe Leu Pro Leu Ile Val Thr Trp 105 Val Leu Val Leu Val Gln Ile Leu Ala Pro Ala Val Ile Asn Asn

120

125

Lys Gly 130

<210> 344

<211> 413

<212> PRT

<213> Escherichia coli

<400> 344

Met Gln Lys His Gly Asp Arg Tyr Val Trp Ile Asn Pro Pro Ala Ile 10 Pro Leu Ser Thr Glu Glu Met Asp Ser Val Phe Ala Leu Pro Tyr Lys Arg Val Pro His Pro Ala Tyr Gly Asn Ala Arg Ile Pro Ala Tyr Glu 40 Met Ile Arg Phe Ser Val Asn Ile Met Arg Gly Cys Phe Gly Gly Cys 55 60 Ser Phe Cys Ser Ile Thr Glu His Glu Gly Arg Ile Ile Gln Ser Arg 75 70 Ser Glu Asp Ser Ile Ile Asn Glu Ile Glu Ala Ile Arg Asp Thr Val 90 Pro Gly Phe Thr Gly Val Ile Ser Asp Leu Gly Gly Pro Thr Ala Asn 105 Met Tyr Met Leu Arg Cys Lys Ser Pro Arg Ala Glu Gln Thr Cys Arg 120 Arg Leu Ser Cys Val Tyr Pro Asp Ile Cys Pro His Met Asp Thr Asn 135 140 His Glu Pro Thr Ile Asn Leu Tyr Arg Arg Ala Arg Asp Leu Lys Gly 150 155 Ile Lys Lys Ile Leu Ile Ala Ser Gly Val Arg Tyr Asp Ile Ala Val 170 Glu Asp Pro Arg Tyr Ile Lys Glu Leu Ala Thr His His Val Gly Gly 185 Tyr Leu Lys Ile Ala Pro Glu His Thr Glu Glu Gly Pro Leu Ser Lys 200

Met Met Lys Pro Gly Met Gly Ser Tyr Asp Arg Phe Lys Glu Leu Phe 215 Asp Thr Tyr Ser Lys Gln Ala Gly Lys Glu Gln Tyr Leu Ile Pro Tyr 230 235 Phe Ile Ser Ala His Pro Gly Thr Arg Asp Glu Asp Met Val Asn Leu 250 245 Ala Leu Trp Leu Lys Lys His Arg Phe Arg Leu Asp Gln Val Gln Asn 260 265 Phe Tyr Pro Ser Pro Leu Ala Asn Ser Thr Thr Met Tyr Tyr Thr Gly 280 285 Lys Asn Pro Leu Ala Lys Ile Gly Tyr Lys Ser Glu Asp Val Phe Val 295 300 Pro Lys Gly Asp Lys Gln Arg Arg Leu His Lys Ala Leu Leu Arg Tyr 315 310 His Asp Pro Ala Asn Trp Pro Leu Ile Arg Gln Ala Leu Glu Ala Met 330 325 Gly Lys Lys His Leu Ile Gly Ser Arg Arg Asp Cys Leu Val Pro Ala 345 340 Pro Thr Ile Glu Glu Met Arg Glu Ala Arg Arg Gln Asn Arg Asn Thr 360 Arg Pro Ala Leu Thr Lys His Thr Pro Met Ala Thr Gln Arg Gln Thr 375 Pro Ala Thr Ala Lys Lys Ala Ser Ser Thr Gln Ser Arg Pro Val Asn 390 395 400 Ala Gly Ala Lys Lys Arg Pro Lys Ala Ala Val Gly Arg

<210> 345

<211> 325 <212> PRT

<213> Escherichia coli

<400> 345

Met Ser Ser Ile Ser Leu Ile Gln Pro Asp Arg Asp Leu Phe Ser Trp 10 Pro Gln Tyr Trp Ala Ala Cys Phe Gly Pro Ala Pro Phe Leu Pro Met 20 25 Ser Arg Glu Glu Met Asp Gln Leu Gly Trp Asp Ser Cys Asp Ile Ile 45 40 Leu Val Thr Gly Asp Ala Tyr Val Asp His Pro Ser Phe Gly Met Ala - 55 Ile Cys Gly Arg Met Leu Glu Ala Gln Gly Phe Arg Val Gly Ile Ile 70 Ala Gln Pro Asp Trp Ser Ser Lys Asp Asp Phe Met Arg Leu Gly Lys Pro Asn Leu Phe Phe Gly Val Thr Ala Gly Asn Met Asp Ser Met Ile 105 110 Asn Arg Tyr Thr Ala Asp Arg Arg Leu Arg His Asp Asp Ala Tyr Thr 120 Pro Asp Asn Val Ala Gly Lys Arg Pro Asp Arg Ala Thr Leu Val Tyr • 135 Thr Gln Arg Cys Lys Glu Ala Trp Lys Asp Val Pro Val Ile Leu Gly 155 150 Gly Ile Glu Ala Ser Leu Arg Arg Thr Ala His Tyr Asp Tyr Trp Ser 170 Asp Thr Val Arg Arg Ser Val Leu Val Asp Ser Lys Ala Asp Met Leu 185 Met Phe Gly Asn Gly Glu Arg Pro Leu Val Glu Val Ala His Arg Leu 200 · Ala Met Gly Glu Pro Ile Ser Glu Ile Arg Asp Val Arg Asn Thr Ala

| Second Second

<210> 346 <211> 226 <212> PRT

<213> Escherichia coli

<400> 346

Met Ile Gln Tyr Leu Asn Val Phe Phe Tyr Asp Ile Tyr Pro Tyr Ile 5 10 Cys Ala Thr Val Phe Phe Leu Gly Ser Trp Leu Arg Tyr Asp Tyr Gly 20 25 Gln Tyr Thr Trp Arg Ala Ser Ser Ser Gln Met Leu Asp Lys Arg Gly 40 Met Val Ile Trp Ser Asn Leu Phe His Ile Gly Ile Leu Gly Ile Phe 55 Phe Gly His Leu Phe Gly Met Leu Thr Pro His Trp Met Tyr Ala Trp 70 75 Phe Leu Pro Val Ala Ala Lys Gln Leu Met Ala Met Val Leu Gly Gly Ile Cys Gly Val Leu Thr Leu Ile Gly Gly Ala Gly Leu Leu Trp Arg 105 Arg Leu Thr Asn Gln Arg Val Arg Ala Thr Ser Thr Thr Pro Asp Ile 120 Ile Ile Met Ser Ile Leu Leu Ile Gln Cys Leu Leu Gly Leu Ser Thr 130 135 Ile Pro Phe Ser Ala Gln Tyr Pro Asp Gly Ser Glu Met Met Lys Leu 145 150 155 160 Val Gly Trp Ala Gln Ser Ile Val Thr Phe Arg Gly Gly Ser Ser Glu 165 170 175 Met Leu Asn Gly Val Ala Phe Val Phe Arg Leu His Leu Val Leu Gly 185 190 Met Thr Ile Phe Leu Leu Phe Pro Phe Thr Arg Leu Val His Val Trp 200 205 Ser Ala Pro Phe Glu Tyr Phe Thr Arg Arg Tyr Gln Ile Val Arg Ser 215 Arg Arg

225

<210> 347 <211> 231 <212> PRT <213> Escherichia coli

<400> 347

Met Gln Ile Leu Lys Val Ile Gly Leu Leu Met Glu Tyr Pro Asp Glu 10 Leu Leu Trp Glu Cys Lys Glu Asp Ala Leu Ala Leu Ile Arg Arg Asp 25 Ala Pro Met Leu Thr Asp Phe Thr His Asn Leu Leu Asn Ala Pro Leu 40 Leu Asp Lys Gln Ala Glu Trp Cys Glu Val Phe Asp Arg Gly Arg Thr 55 Thr Ser Leu Leu Phe Glu His Val His Ala Glu Ser Arg Asp Arg 70 75 Gly Gln Ala Met Val Asp Leu Leu Ala Glu Tyr Glu Lys Val Gly Leu 85 90 Gln Leu Asp Cys Arg Glu Leu Pro Asp Tyr Leu Pro Leu Tyr Leu Glu 100 105 Tyr Leu Ser Val Leu Pro Asp Asp Gln Ala Lys Glu Gly Leu Leu Asn 120 125 Val Ala Pro Ile Leu Ala Leu Leu Gly Gly Arg Leu Lys Gln Arg Glu 135 140 Ala Pro Trp Tyr Ala Leu Phe Asp Ala Leu Leu Gln Leu Ala Gly Ser 155 150 Ser Leu Ser Ser Asp Ser Val Thr Lys Gln Val Asn Ser Glu Glu Arg 165 170 Asp Asp Thr Arg Gln Ala Leu Asp Ala Val Trp Glu Glu Glu Gln Val 180 185 190 Lys Phe Ile Glu Asp Asn Ala Thr Ala Cys Asp Ser Ser Pro Leu Asn 195 200 205 Gln Tyr Gln Arg Arg Phe Ser Gln Asp Val Ala Pro Gln Tyr Val Asp 215 220 Ile Ser Ala Gly Gly Gly Lys

<210> 348

<211> 514

<212> PRT

<213> Escherichia coli

<400> 348

Met Lys Ile Arg Ser Gln Val Gly Met Val Leu Asn Leu Asp Lys Cys 10 Ile Gly Cys His Thr Cys Ser Val Thr Cys Lys Asn Val Trp Thr Gly 25 Arg Glu Gly Met Glu Tyr Ala Trp Phe Asn Asn Val Glu Thr Lys Pro 40 Gly Ile Gly Tyr Pro Lys Asn Trp Glu Asp Gln Glu Glu Trp Gln Gly 55 Gly Trp Val Arg Asp Val Asn Gly Lys Ile Arg Pro Arg Leu Gly Asn 70 Lys Met Gly Val Ile Thr Lys Ile Phe Ala Asn Pro Val Val Pro Gln 90 Ile Asp Asp Tyr Tyr Glu Pro Phe Thr Phe Asp Tyr Glu His Leu His 1.00 105 Ser Ala Pro Glu Gly Lys His Ile Pro Thr Ala Arg Pro Arg Ser Leu 120 125 Ile Asp Gly Lys Arg Met Asp Lys Val Ile Trp Gly Pro Asn Trp Glu 135 140 Glu Leu Leu Gly Gly Glu Phe Glu Lys Arg Ala Arg Asp Arg Asn Phe 150 155 Glu Ala Met Gln Lys Glu Met Tyr Gly Gln Phe Glu Asn Thr Phe Met 165 170 Met Tyr Leu Pro Arg Leu Cys Glu His Cys Leu Asn Pro Ser Cys Val

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185
           180
Ala Thr Cys Pro Ser Gly Ala Ile Tyr Lys Arg Glu Glu Asp Gly Ile
                          200
Val Leu Ile Asp Gln Asp Lys Cys Arg Gly Trp Arg Leu Cys Ile Ser
                                          220
                       215
Gly Cys Pro Tyr Lys Lys Ile Tyr Phe Asn Trp Lys Ser Gly Lys Ser
                   230
                                      235
Glu Lys Cys Ile Phe Cys Tyr Pro Arg Ile Glu Ser Gly Gln Pro Thr
               245 .
                           250
Val Cys Ser Glu Thr Cys Val Gly Arg Ile Arg Tyr Leu Gly Val Leu
                               265
Leu Tyr Asp Ala Asp Arg Ile Glu Glu Ala Ala Ser Thr Glu Arg Glu
                           280
Val Asp Leu Tyr Glu Arg Gln Cys Glu Val Phe Leu Asp Pro His Asp
                                          300
                       295
Pro Ser Val Ile Glu Glu Ala Leu Lys Gln Gly Ile Pro Gln Asn Val
                   310
                                       315
Ile Asp Ala Ala Gln Arg Ser Pro Val Tyr Lys Met Ala Met Asp Trp
               325
                                   330
Lys Leu Ala Leu Pro Leu His Pro Glu Tyr Arg Thr Leu Pro Met Val
                              345
Trp Tyr Val Pro Pro Leu Ser Pro Ile Gln Ser Tyr Ala Asp Ala Gly
                           360
Gly Leu Pro Lys Ser Glu Gly Val Leu Pro Ala Ile Glu Ser Leu Arg
                      375
                                          380
Ile Pro Val Gln Tyr Leu Ala Asn Met Leu Ser Ala Gly Asp Thr Gly
                  390
                                       395
Pro Val Leu Arg Ala Leu Lys Arg Met Met Ala Met Arg His Tyr Met
               405
                                  410
Arg Ser Gln Thr Val Glu Gly Val Thr Asp Thr Arg Ala Ile Asp Glu
                                                .430
          420
                              425
Val Gly Leu Ser Val Ala Gln Val Glu Glu Met Tyr Arg Tyr Leu Ala
                          440
Ile Ala Asn Tyr Glu Asp Arg Phe Val Ile Pro Thr Ser His Arg Glu
                      455
Met Ala Gly Asp Ala Phe Ala Glu Arg Asn Gly Cys Gly Phe Thr Phe
                   470
                                      475
Gly Asp Gly Cys His Gly Ser Asp Ser Lys Phe Asn Leu Phe Asn Ser
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Ser Arg Ile Asp Ala Ile Asn Ile Thr Glu Val Arg Asp Lys Ala Glu
                              505
Gly Glu
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<210> 349 <211> 1246

<212> PRT

<213> Escherichia coli

## <400> 349

 Met
 Ser
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 Leu
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 Arg
 Phe
 Arg
 Tyr
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 Lys
 Gln
 Lys
 Gly
 Glu
 15

 Thr
 Phe
 Ala
 Asp
 Gly
 His
 Gly
 Gln
 Val
 Met
 His
 Ser
 Asp
 Asp
 Asp
 Trp

 Glu
 Asp
 Ser
 Tyr
 Arg
 Gln
 Arg
 Trp
 Gln
 Phe
 Asp
 Lys
 Ile
 Val
 Arg
 Ser

 Glu
 Asp
 Ser
 Tyr
 Arg
 Gln
 Phe
 Asp
 Lys
 Ile
 Val
 Arg
 Ser

 Thr
 His
 Gly
 Val
 Asn
 Cys
 Thr
 Gly
 Ser
 Cys
 Ser
 Trp
 Lys
 Ile
 Tyr
 Val

 Asp
 Gly
 Leu
 Val
 Thr
 Trp
 Glu
 Ile
 Gln
 Thr
 Asp
 Tyr
 Pro
 Arg

Thr	Arg	Pro	Asp	Leu 85	Pro	Asn	His	Glu	Pro 90	Arg	Gly	Cys	Pro	Arg 95	Gly
Ala	Ser	Tyr	Ser	Trp	Tyr	Leu	Tyr	Ser 105	Ala	Asn	Arg	Leu	Lys 110	Tyr	Pro
Leu	Ile	Arg 115		Arg	Leu	Ile	Glu 120	Leu	Trp	Arg	Glu	Ala 125		Lys	Gln
His	Ser 130		Pro	Val	Leu	Ala 135		Ala	Ser	Ile	Met 140		Asp	Pro	Gln
Lys 145		Leu	Ser	Tyr	Lys 150		Val	Arg	Gly	Arg		Gly	Phe	Ile	Arg 160
	Asn	Trp	Gln	Glu 165	-	Asn	Gln	Leu	Ile 170		Ala	Ala	Asn	Val 175	
Thr	Ile	Lys	Thr 180		Gly	Pro	Asp	Arg 185		Ala	Gly	Phe	Ser		Ile
Pro	Ala	Met 195		Met	Val	Ser	Tyr 200	Ala	Ala	Gly	Thr	Arg 205		Leu	Ser
Leu	Leu 210		Gly	Thr	Cys	Leu 215		Phe	Tyr	Asp	Trp 220		Сув	Asp	Leu
Pro 225		Ala	Ser	Pro	Met 230	_	Trp	Gly	Glu	Gln 235		Asp	Val	Pro	Glu 240
	Ala	Asp	Trp	Tyr 245		Ser	Ser	Tyr	Ile 250		Ala	Trp	Gly	Ser 255	
Val	Pro	Gln	Thr 260		Thr	Pro	Asp	Ala 265		Phe	Phe	Thr	Glu 270		Arg
Tyr	Lys	Gly 275		Lys	Thr	Ile	Ala 280	Ile	Thr	Pro	Asp	Tyr 285		Glu	Val
Ala	Lys 290		Сув	qaA	Gln	Trp 295	Leu	Ala	Pro	Lys	Gln 300	Gly	Thr	Asp	Ser
Ala 305	Leu	Ala	Met	Ala	Met 310	Gly	His	Val	Ile	Leu 315	Lys	Glu	Phe	His	Leu 320
Asp	Asn	Pro	Ser	Asp 325	Tyr	Phe	Ile	Asn	Tyr 330	_	Arg	Arg	Tyr	Ser 335	qaA
Met	Pro	Met	Leu 340	Val	Met	Leu	Glu	Pro 345	Arg	Asp	Asp	Gly	Ser 350	Tyr	Val
Pro	Gly	Arg 355	Met	Ile	Arg	Ala	Ser 360	Asp	Leu	Val	Asp	Gly 365	Leu	Gly	Glu
Ser	Asn 370	Asn	Pro	Gln	Trp	Lys 375	Thr	Val	Ala	Val	Asn 380	Thr	Ala	Gly	Glu
Leu 385	Val	Val	Pro		Gly 390	Ser	Ile	Gly	Phe	Arg 395	Trp	Gly	Glu	Lys	Gly 400
Lys	_			405				Ala	410					415	
Leu	Thr	Leu	Leu 420	Gly	Gln	His	Asp	Ala 425	Val	Ala	Gly	Val	Ala 430	Phe	Pro
Tyr	Phe	Gly 435	Gly	Ile	Glu	Asn	Pro 440	His	Phe	Arg	Ser	Val 445	Lys	His	Asn
Pro	Val 450	Leu	Val	Arg	Gln	Leu 455	Pro	Val	Lys	Asn	Leu 460	Thr	Leu	Val	Asp
Gly 465	Asn	Thr	Сув	Pro	Val 470	Val	Ser	Val	Tyr	Asp 475	Leu	Val	Leu	Ala	Asn 480
Tyr	Gly	Leu	Asp	Arg 485	_	Leu	Glu	Asp	Glu 490	Asn	Ser	Ala	Lys	Asp 495	Tyr
Ala	Glu	Ile	<b>Lys</b> 500	Pro	Tyr	Thr	Pro	Ala 505	Trp	Gly	Glu	Gln	Ile 510	Thr	Gly
Val	Pro	Arg 515	Gln	Туг	Ile	Glu	Thr 520	Ile	Ala	Arg	Glu	Phe 525	Ala	Asp	Thr
Ala	His 530	Lуз	Thr	His	Gly	Arg 535	Ser	Met	Ile	Ile	Leu 540	Gly	Ala	Gly	Val
Asn 545	His	Trp	Tyr	His	Met 550	Asp	Met	Asn	Tyr	Arg 555	Gly	Met	Ile	Asn	Met 560
Leu	Ile	Phe	Суз	Gly	Суз	Val	Gly	Gln	Ser	Gly	Gly	Gly	Trp	Ala	His

				565					E 7.0					<b>5</b> 75	
የ	Val	Glv	Gln		Lvs	T.e.11	Ανα	Pro	570	Thr	GIV	TTT	Len	575 Pro	Len
			580					585					590		
Ala	Phe	Ala 595	Leu	Asp	Trp	Asn	Arg 600	Pro	Pro	Arg	Gln	Met 605	Asn	Ser	Thr
Ser	Phe 610	Phe	Tyr	Asn	His	Ser 615	Ser	Gln	Trp	Arg	Tyr 620	Glu	Lys	Val	Ser
Ala 625	Gln	Glu	Leu	Leu	Ser 630	Pro	Leu	Ala	Asp	Ala 635	Ser	Lys	Tyr	Ser	Gly 640
	Leu	Ile	Asp			Val	Arg	Ala		Arg	Met	Gly	Trp		
Ser	Ala	Pro		645 Leu	Gly	Arg	Asn		650 Leu	Gly	Ile	Lys		655 Glu	Ala
Asp	Lys	Ala	660 Gly	Leu	Ser	Pro	Thr	665 Glu	Phe	Thr	Ala	Gln	670 Ala	Leu	Lys
Ser	Glv	675 Asp	Leu	Arq	Met	Ala	680 Cvs	Glu	Gln	Pro	Asp	685 Ser	Ser	Ser	Asn
	690	_				695	_				700				
705					710			_		Asn 715			_		720
Gly	Lys	Gly	His	Glu 725	Tyr	Met	Gln	Lys	Tyr 730	Leu	Leu	Gly	Thr	Glu 735	Ser
Gly	Ile	Gln	Gly 740	Glu	Glu	Leu	Gly	Ala 745	Ser	Asp	Gly	Ile	Lys 750	Pro	Glu
Glu	Val	Glu 755	Trp	Gln	Thr	Ala	Ala 760	Ile	Glu	Gly	ГЛЗ	Leu 765	Asp	Leu	Leu
Val	Thr 770		qaA	Phe	Arg	Met 775		Ser	Thr	Cys	Leu 780		Ser	Asp	Ile
Val 785		Pro	Thr	Ala	Thr 790		Тух	Glu	Lys	Asp 795		Met	Asn	Thr	Ser 800
	Met	His	Pro			His	Pro	Leu		Ala	Ala	Val	Asp		
Trp	Glu	Ser		805 Ser	Asp	Trp	Glu		810 Tyr	Lys	Gly	Ile		815 Lys	Ala
Phe	Ser		820 Val	Cys	Val	Gly		825 Leu	Gly	Lys	Glu		0E8 QaA	Val	Val
Ьeu	Gln	835 Pro	Leu	Leu	His	Asp	840 Ser	Pro	Ala	Glu	Leu	845 Ser	Gln	Pro	Cys
	850					855					860				-
865			-	_	870	-	-		-	Asp 875				_	880
Thr	Ala	Pro	Asn	Ile 885	Val	Ala	Val	Glu	Arg 890	Asp	Tyr	Pro	Ala	Thr 895	Tyr
Glu	Arg	Phe	Thr 900	Ser	Leu	Gly	Pro	Leu 905	Met	Asp	Lys	Leu	Gly 910	Asn	Gly
Gly	Lys	Gly 915	Ile	Ser	Trp	Asn	Thr 920	Gln	Asp	Glu	Ile	Asp 925	Phe	Leu	Gly
Lys	Leu 930	Asn	Tyr	Thr	Lys	Arg 935	Asp	Gly	Pro	Ala	Gln 940	Gly	Arg	Pro	Leu
	Asp	Thr	Ala	Ile			Ser	Glu	Val	Ile		Ala	Leu	Ala	
945 Glu	Thr	Asn	Gly	His	950 Val	Ala	Val	Lys	Ala	955 Trp	Gln	Ala	Leu	_	960 Glu
Ile	Thr	Gly	Arg	965 Glu	His	Thr	His	Leu	970 Ala	Leu	His	Lys	Glu	975 Asp	Glu
Lys	Ile	Arg	980 Phe	Arg	Asp	Ile	Gln	985 Ala	Gln	Pro	Arg	Lys	990 Ile	Ile	Ser
		995					1000	)				1005	5		
	1010	)				1015	5			His	1020	)			
Gly 1025		Thr	Asn	Val			Leu	Ile	Pro	Trp		Thr	Leu	Ser	
		Gln	Leu	_			His	Pro	-	Met		Ala	Phe	-	
				1045	•				1050	,				1055	•

- [

Ser Leu Val Ala Tyr Arg Pro Pro Ile Asp Thr Arg Ser Val Ser Glu 1060 · 1065 Met Arg Gln Ile Pro Pro Asn Gly Phe Pro Glu Lys Ala Leu Asn Phe 1075 1080 1085 Leu Thr Pro His Gln Lys Trp Gly Ile His Ser Thr Tyr Ser Glu Asn 1090 1095 1100 Leu Leu Met Leu Thr Leu Ser Arg Gly Gly Pro Ile Val Trp Ile Ser 1105 1110 1115 1120 Glu Thr Asp Ala Arg Glu Leu Thr Ile Val Asp Asn Asp Trp Val Glu 1125 1130 1135 Val Phe Asn Ala Asn Gly Ala Leu Thr Ala Arg Ala Val Val Ser Gln 1145 1150 1140 Arg Val Pro Pro Gly Met Thr Met Met Tyr His Ala Gln Glu Arg Ile 1155 1160 1165 Met Asn Ile Pro Gly Ser Glu Val Thr Gly Met Arg Gly Gly Ile His 1170 1175 1180 Asn Ser Val Thr Arg Val Cys Pro Lys Pro Thr His Met Ile Gly Gly 1185 1190 1195 Tyr Ala Gln Leu Ala Trp Gly Phe Asn Tyr Tyr Gly Thr Val Gly Ser 1205 1210 1215 Asn Arg Asp Glu Phe Ile Met Ile Arg Lys Met Lys Asn Val Asn Trp 1220 1225 Leu Asp Asp Glu Gly Arg Asp Gln Val Gln Glu Ala Lys Lys 1235 1240 .

<210> 350 <211> 165 <212> PRT

<213> Escherichia coli

<400> 350

Met Asp Leu Ser Gln Leu Thr Pro Arg Arg Pro Tyr Leu Leu Arg Ala 1 5 10 . 15 Phe Tyr Glu Trp Leu Leu Asp Asn Gln Leu Thr Pro His Leu Val Val 25 Asp Val Thr Leu Pro Gly Val Gln Val Pro Met Glu Tyr Ala Arg Asp 40 Gly Gln Ile Val Leu Asn Ile Ala Pro Arg Ala Val Gly Asn Leu Glu 55 Leu Ala Asn Asp Glu Val Arg Phe Asn Ala Arg Phe Gly Gly Ile Pro 70 75 Arg Gln Val Ser Val Pro Leu Ala Ala Val Leu Ala Ile Tyr Ala Arg 85 90 Glu Asn Gly Ala Gly Thr Met Phe Glu Pro Glu Ala Ala Tyr Asp Glu 105 Asp Thr Ser Ile Met Asn Asp Glu Glu Ala Ser Ala Asp Asn Glu Thr 120 Val Met Ser Val Ile Asp Gly Asp Lys Pro Asp His Asp Asp Asp Thr 135 140 His Pro Asp Asp Glu Pro Pro Gln Pro Pro Arg Gly Gly Arg Pro Ala 150 155 Leu Arg Val Val Lys

<210> 351 <211> 212

.010. 222

<212> PRT

<213> Escherichia coli

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<210> 352

<211> 505

<212> PRT

<213> Escherichia coli

<400> 352

Met Ser Glu. Gln His Ala Gln Gly Ala Asp Ala Val Val Asp Leu Asn Asn Glu Leu Lys Thr Arg Arg Glu Lys Leu Ala Asn Leu Arg Glu Gln Gly Ile Ala Phe Pro Asn Asp Phe Arg Arg Asp His Thr Ser Asp Gln 40 Leu His Ala Glu Phe Asp Gly Lys Glu Asn Glu Glu Leu Glu Ala Leu Asn Ile Glu Val Ala Val Ala Gly Arg Met Met Thr Arg Arg Ile Met 70 75 Gly Lys Ala Ser Phe Val Thr Leu Gln Asp Val Gly Gly Arg Ile Gln 90 Leu Tyr Val Ala Arg Asp Asp Leu Pro Glu Gly Val Tyr Asn Glu Gln 105 Phe Lys Lys Trp Asp Leu Gly Asp Ile Leu Gly Ala Lys Gly Lys Leu 115 " 120 Phe Lys Thr Lys Thr Gly Glu Leu Ser Ile His Cys Thr Glu Leu Arg 135 Leu Leu Thr Lys Ala Leu Arg Pro Leu Pro Asp Lys Phe His Gly Leu 150 155 Gln Asp Gln Glu Ala Arg Tyr Arg Gln Arg Tyr Leu Asp Leu Ile Ser 170 Asn Asp Glu Ser Arg Asn Thr Phe Lys Val Arg Ser Gln Ile Leu Ser 180 185

```
Gly Ile Arg Gln Phe Met Val Asn Arg Gly Phe Met Glu Val Glu Thr
                           200
Pro Met Met Gln Val Ile Pro Gly Gly Ala Ala Arg Pro Phe Ile
                       215
Thr His His Asn Ala Leu Asp Leu Asp Met Tyr Leu Arg Ile Ala Pro
                   230
                                       235
Glu Leu Tyr Leu Lys Arg Leu Val Val Gly Gly Phe Glu Arg Val Phe
              245
                                   250
Glu Ile Asn Arg Asn Phe Arg Asn Glu Gly Ile Ser Val Arg His Asn
                            265
Pro Glu Phe Thr Met Met Glu Leu Tyr Met Ala Tyr Ala Asp Tyr Lys
                          280
Asp Leu Ile Glu Leu Thr Glu Ser Leu Phe Arg Thr Leu Ala Gln Asp
                       295
                                           300
Ile Leu Gly Lys Thr Glu Val Thr Tyr Gly Asp Val Thr Leu Asp Phe
                   310
                                       315
Gly Lys Pro Phe Glu Lys Leu Thr Met Arg Glu Ala Ile Lys Lys Tyr
                                  330
               325
Arg Pro Glu Thr Asp Met Ala Asp Leu Asp Asn Phe Asp Ser Ala Lys
           340
                              345
Ala Ile Ala Glu Ser Ile Gly Ile His Val Glu Lys Ser Trp Gly Leu
                           360
Gly Arg Ile Val Thr Glu Ile Phe Glu Glu Val Ala Glu Ala His Leu
                       375
                                           380
Ile Gln Pro Thr Phe Ile Thr Glu Tyr Pro Ala Glu Val Ser Pro Leu
                                       395
Ala Arg Arg Asn Asp Val Asn Pro Glu Ile Thr Asp Arg Phe Glu Phe
              405
                                  410
Phe Ile Gly Gly Arg Glu Ile Gly Asn Gly Phe Ser Glu Leu Asn Asp
                              425
Ala Glu Asp Gln Ala Gln Arg Phe Leu Asp Gln Val Ala Ala Lys Asp
                           440
Ala Gly Asp Asp Glu Ala Met Phe Tyr Asp Glu Asp Tyr Val Thr Ala
                      455
Leu Glu His Gly Leu Pro Pro Thr Ala Gly Leu Gly Ile Gly Ile Asp
                  470
                                       475
Arg Met Val Met Leu Phe Thr Asn Ser His Thr Ile Arg Asp Val Ile
               485
                                   490
Leu Phe Pro Ala Met Arg Pro Val Lys
           500
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<210> 353

<211> 365

<212> PRT

<213> Escherichia coli

<400> 353

 Met
 Phe
 Glu
 Ile
 Asn
 Pro
 Val
 Asn
 Asn
 Asn
 Arg
 Ile
 Glu
 Asp
 Leu
 Thr
 Glu

 Arg
 Ser
 Asp
 Val
 Leu
 Arg
 Gly
 Tyr
 Leu
 Asp
 Tyr
 Asp
 Tyr
 Asp
 Asp
 Tyr
 Asp
 Tyr
 Asp
 Asp
 Tyr
 Asp
 Asp
 Tyr
 Asp
 Asp
 Tyr
 Asp
 Asp

105 Leu Glu Phe Arg Arg Met Phe Ser Gly Glu Tyr Asp Ser Ala Asp Cys . 115 120 Tyr Leu Asp Ile Gln Ala Gly Ser Gly Gly Thr Glu Ala Gln Asp Trp 135 140 Ala Ser Met Leu Glu Arg Met Tyr Leu Arg Trp Ala Glu Ser Arg Gly 150 155 Phe Lys Thr Glu Ile Ile Glu Glu Ser Glu Gly Glu Val Ala Gly Ile 165 170 Lys Ser Val Thr Ile Lys Ile Ser Gly Asp Tyr Ala Tyr Gly Trp Leu 185 Arg Thr Glu Thr Gly Val His Arg Leu Val Arg Lys Ser Pro Phe Asp 200 Ser Gly Gly Arg Arg His Thr Ser Phe Ser Ser Ala Phe Val Tyr Pro 215 220 Glu Val Asp Asp Asp Ile Asp Ile Glu Ile Asn Pro Ala Asp Leu Arg 230 235 Ile Asp Val Tyr Arg Thr Ser Gly Ala Gly Gly Gln His Val Asn Arg 245 250 Thr Glu Ser Ala Val Arg Ile Thr His Ile Pro Thr Gly Ile Val Thr 265 Gln Cys Gln Asn Asp Arg Ser Gln His Lys Asn Lys Asp Gln Ala Met 280 285 Lys Gln Met Lys Ala Lys Leu Tyr Glu Leu Glu Met Gln Lys Lys Asn 295 300 Ala Glu Lys Gln Ala Met Glu Asp Asn Lys Ser Asp Ile Gly Trp Gly 310 315 Ser Gln Ile Arg Ser Tyr Val Leu Asp Asp Ser Arg Ile Lys Asp Leu 330 325 Arg Thr Gly Val Glu Thr Arg Asn Thr Gln Ala Val Leu Asp Gly Ser 345 Leu Asp Gln Phe Ile Glu Ala Ser Leu Lys Ala Gly Leu 360

<210> 354

<211> 577

<212> PRT

<213> Escherichia coli

<400> 354

Met Lys Gln Gln Ile Gln Leu Arg Arg Glu Val Asp Glu Thr Ala Asp Leu Pro Ala Glu Leu Pro Pro Leu Leu Arg Arg Leu Tyr Ala Ser 25 Arg Gly Val Arg Ser Ala Gln Glu Leu Glu Arg Ser Val Lys Gly Met Leu Pro Trp Gln Gln Leu Ser Gly Val Glu Lys Ala Val Glu Ile Leu Tyr Asn Ala Phe Arg Glu Gly Thr Arg Ile Ile Val Val Gly Asp Phe 70 Asp Ala Asp Gly Ala Thr Ser Thr Ala Leu Ser Val Leu Ala Met Arg 90 Ser Leu Gly Cys Ser Asn Ile Asp Tyr Leu Val Pro Asn Arg Phe Glu 105 Asp Gly Tyr Gly Leu Ser Pro Glu Val Val Asp Gln Ala His Ala Arg 120 Gly Ala Gln Leu Ile Val Thr Val Asp Asn Gly Ile Ser Ser His Ala 135 Gly Val Glu His Ala Arg Ser Leu Gly Ile Pro Val Ile Val Thr Asp

```
His His Leu Pro Gly Asp Thr Leu Pro Ala Ala Glu Ala Ile Ile Asn
              165
                                 170
Pro Asn Leu Arg Asp Cys Asn Phe Pro Ser Lys Ser Leu Ala Gly Val
                              185
Gly Val Ala Phe Tyr Leu Met Leu Ala Leu Arg Thr Phe Leu Arg Asp
                          200
Gln Gly Trp Phe Asp Glu Arg Asn Ile Ala Ile Pro Asn Leu Ala Glu
                      215
                                          220
Leu Leu Asp Leu Val Ala Leu Gly Thr Val Ala Asp Val Val Pro Leu
                  230
                                      235
Asp Ala Asn Asn Arg Ile Leu Thr Trp Gln Gly Met Ser Arg Ile Arg
              245
                                  250
Ala Gly Lys Cys Arg Pro Gly Ile Lys Ala Leu Leu Glu Val Ala Asn
  · 260
                              265
Arg Asp Ala Gln Lys Leu Ala Ala Ser Asp Leu Gly Phe Ala Leu Gly
      275
                          280
Pro Arg Leu Asn Ala Ala Gly Arg Leu Asp Asp Met Ser Val Gly Val
                      295
Ala Leu Leu Cys Asp Asn Ile Gly Glu Ala Arg Val Leu Ala Asn
                  310
Glu Leu Asp Ala Leu Asn Gln Thr Arg Lys Glu Ile Glu Gln Gly Met
              325
                                  330
Gln Ile Glu Ala Leu Thr Leu Cys Glu Lys Leu Glu Arg Ser Arg Asp
                             345
Thr Leu Pro Gly Gly Leu Ala Met Tyr His Pro Glu Trp His Gln Gly
       355
                          360
                                             365
Val Val Gly Ile Leu Ala Ser Arg Ile Lys Glu Arg Phe His Arg Pro
                      375
                                         380
Val Ile Ala Phe Ala Pro Ala Gly Asp Gly Thr Leu Lys Gly Ser Gly
                  390
                                      395
Arg Ser Ile Gln Gly Leu His Met Arg Asp Ala Leu Glu Arg Leu Asp
              405
                                  410
Thr Leu Tyr Pro Gly Met Met Leu Lys Phe Gly Gly His Ala Met Ala
                             425
          420
Ala Gly Leu Ser Leu Glu Glu Asp Lys Phe Lys Leu Phe Gln Gln Arg
                          440
Phe Gly Glu Leu Val Thr Glu Trp Leu Asp Pro Ser Leu Leu Gln Gly
                      455
                                         460
Glu Val Val Ser Asp Gly Pro Leu Ser Pro Ala Glu Met Thr Met Glu
                                     475
Val Ala Gln Leu Leu Arg Asp Ala Gly Pro Trp Gly Gln Met Phe Pro
                                 490
Glu Pro Leu Phe Asp Gly His Phe Arg Leu Leu Gln Gln Arg Leu Val
                          505
Gly Glu Arg His Leu Lys Val Met Val Glu Pro Val Gly Gly Pro
                       520
Leu Leu Asp Gly Ile Ala Phe Asn Val Asp Thr Ala Leu Trp Pro Asp
                      535
                                         540
Asn Gly Val Arg Glu Val Gln Leu Ala Tyr Lys Leu Asp Ile Asn Glu
                                     555
                  550
Phe Arg Gly Asn Arg Ser Leu Gln Ile Ile Ile Asp Asn Ile Trp Pro
               565
                                  570
Ile
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<210> 355

<211> 236

<212> PRT

<213> Escherichia coli

Met Lys Lys Gly Phe Met Leu Phe Thr Leu Leu Ala Ala Phe Ser Gly 10 Phe Ala Gln Ala Asp Asp Ala Ala Ile Gln Gln Thr Leu Ala Lys Met 25 Gly Ile Lys Ser Ser Asp Ile Gln Pro Ala Pro Val Ala Gly Met Lys 40 Thr Val Leu Thr Asn Ser Gly Val Leu Tyr Ile Thr Asp Asp Gly Lys 55 His Ile Ile Gln Gly Pro Met Tyr Asp Val Ser Gly Thr Ala Pro Val 70 75 Asn Val Thr Asn Lys Met Leu Leu Lys Gln Leu Asn Ala Leu Glu Lys 85 90 Glu Met Ile Val Tyr Lys Ala Pro Gln Glu Lys His Val Ile Thr Val 105 Phe Thr Asp Ile Thr Cys Gly Tyr Cys His Lys Leu His Glu Gln Met 120 125 Ala Asp Tyr Asn Ala Leu Gly Ile Thr Val Arg Tyr Leu Ala Phe Pro 135 140 Arg Gln Gly Leu Asp Ser Asp Ala Glu Lys Glu Met Lys Ala Ile Trp 150 155 Cys Ala Lys Asp Lys Asn Lys Ala Phe Asp Asp Val Met Ala Gly Lys 165 170 Ser Val Ala Pro Ala Ser Cys Asp Val Asp Ile Ala Asp His Tyr Ala 185 180 Leu Gly Val Gln Leu Gly Val Ser Gly Thr Pro Ala Val Val Leu Ser 195 200 Asn Gly Thr Leu Val Pro Gly Tyr Gln Pro Pro Lys Glu Met Lys Glu 215 Phe Leu Asp Glu His Gln Lys Met Thr Ser Gly Lys 230

<210> 356 <211> 298

<212> PRT

<213> Escherichia coli

<400> 356

Met Lys Gln Asp Leu Ala Arg Ile Glu Gln Phe Leu Asp Ala Leu Trp 10 Leu Glu Lys Asn Leu Ala Glu Asn Thr Leu Asn Ala Tyr Arg Arg Asp 25 Leu Ser Met Met Val Glu Trp Leu His His Arg Gly Leu Thr Leu Ala 40 Thr Ala Gln Ser Asp Asp Leu Gln Ala Leu Leu Ala Glu Arg Leu Glu 55 Gly Gly Tyr Lys Ala Thr Ser Ser Ala Arg Leu Leu Ser Ala Val Arg Arg Leu Phe Gln Tyr Leu Tyr Arg Glu Lys Phe Arg Glu Asp Asp Pro 90 Ser Ala His Leu Ala Ser Pro Lys Leu Pro Gln Arg Leu Pro Lys Asp 105 Leu Ser Glu Ala Gln Val Glu Arg Leu Leu Gln Ala Pro Leu Ile Asp 120 Gln Pro Leu Glu Leu Arg Asp Lys Ala Met Leu Glu Val Leu Tyr Ala 135 140 Thr Gly Leu Arg Val Ser Glu Leu Val Gly Leu Thr Met Ser Asp Ile 155 160 Ser Leu Arg Gln Gly Val Val Arg Val Ile Gly Lys Gly Asn Lys Glu

Arg Leu Val Pro Leu Gly Glu Glu Ala Val Tyr Trp Leu Glu Thr Tyr 185 180 Leu Glu His Gly Arg Pro Trp Leu Leu Asn Gly Val Ser Ile Asp Val 200 Leu Phe Pro Ser Gln Arg Ala Gln Gln Met Thr Arg Gln Thr Phe Trp 215 220 His Arg Ile Lys His Tyr Ala Val Leu Ala Gly Ile Asp Ser Glu Lys 230 235 Leu Ser Pro His Val Leu Arg His Ala Phe Ala Thr His Leu Leu Asn 245 250 His Gly Ala Asp Leu Arg Val Val Gln Met Leu Leu Gly His Ser Asp 260 265 . Leu Ser Thr Thr Gln Ile Tyr Thr His Val Ala Thr Glu Arg Leu Arg 280 275 Gln Leu His Gln Gln His His Pro Arg Ala

<210> 357

<211> 367

<212> PRT

<213> Escherichia coli

<400> 357

Met Ser Asp Ser Gln Thr Leu Val Val Lys Leu Gly Thr Ser Val Leu 10 Thr Gly Gly Ser Arg Arg Leu Asn Arg Ala His Ile Val Glu Leu Val 25 Arg Gln Cys Ala Gln Leu His Ala Ala Gly His Arg Ile Val Ile Val 40 Thr Ser Gly Ala Ile Ala Ala Gly Arg Glu His Leu Gly Tyr Pro Glu 55 Leu Pro Ala Thr Ile Ala Ser Lys Gln Leu Leu Ala Ala Val Gly Gln 70 75 Ser Arg Leu Ile Gln Leu Trp Glu Gln Leu Phe Ser Ile Tyr Gly Ile His Val Gly Gln Met Leu Leu Thr Arg Ala Asp Met Glu Asp Arg Glu 105 Arg Phe Leu Asn Ala Arg Asp Thr Leu Arg Ala Leu Leu Asp Asn Asn 120 125 Ile Val Pro Val Ile Asn Glu Asn Asp Ala Val Ala Thr Ala Glu Ile 135 Lys Val Gly Asp Asn Asp Asn Leu Ser Ala Leu Ala Ala Ile Leu Ala 150 155 160 Gly Ala Asp Lys Leu Leu Leu Thr Asp Gln Lys Gly Leu Tyr Thr 165 170 175 Ala Asp Pro Arg Ser Asn Pro Gln Ala Glu Leu Ile Lys Asp Val Tyr 170 175 180 185 190 Gly Ile Asp Asp Ala Leu Arg Ala Ile Ala Gly Asp Ser Val Ser Gly 200 Leu Gly Thr Gly Gly Met Ser Thr Lys Leu Gln Ala Ala Asp Val Ala 220 215 Cys Arg Ala Gly Ile Asp Thr Ile Ile Ala Ala Gly Ser Lys Pro Gly 235 240 230 Val Ile Gly Asp Val Met Glu Gly Ile Ser Val Gly Thr Leu Phe His 245 250 Ala Gln Ala Thr Pro Leu Glu Asn Arg Lys Arg Trp Ile Phe Gly Ala 265 Pro Pro Ala Gly Glu Ile Thr Val Asp Glu Gly Ala Thr Ala Ala Ile 280 Leu Glu Arg Gly Ser Ser Leu Leu Pro Lys Gly Ile Lys Ser Val Thr

<210> 358 <211> 417 <212> PRT <213> Escherichia coli

<400> 358

Met Leu Glu Gln Met Gly Ile Ala Ala Lys Gln Ala Ser Tyr Lys Leu 10 Ala Gln Leu Ser Ser Arg Glu Lys Asn Arg Val Leu Glu Lys Ile Ala 20 25 Asp Glu Leu Glu Ala Gln Ser Glu Ile Ile Leu Asn Ala Asn Ala Gln 40 Asp Val Ala Asp Ala Arg Ala Asn Gly Leu Ser Glu Ala Met Leu Asp 55 Arg Leu Ala Leu Thr Pro Ala Arg Leu Lys Gly Ile Ala Asp Asp Val 75 Arg Gln Val Cys Asn Leu Ala Asp Pro Val Gly Gln Val Ile Asp Gly 90 Gly Val Leu Asp Ser Gly Leu Arg Leu Glu Arg Arg Arg Val Pro Leu 105 Gly Val Ile Gly Val Ile Tyr Glu Ala Arg Pro Asn Val Thr Val Asp 120 Val Ala Ser Leu Cys Leu Lys Thr Gly Asn Ala Val Ile Leu Arg Gly 135 140 Gly Lys Glu Thr Cys Arg Thr Asn Ala Ala Thr Val Ala Val Ile Gln 150 155 Asp Ala Leu Lys Ser Cys Gly Leu Pro Ala Gly Ala Val Gln Ala Ile 170 165 Asp Asn Pro Asp Arg Ala Leu Val Ser Glu Met Leu Arg Met Asp Lys 180 185 Tyr Ile Asp Met Leu Ile Pro Arg Gly Gly Ala Gly Leu His Lys Leu 200 Cys Arg Glu Gln Ser Thr Ile Pro Val Ile Thr Gly Gly Ile Gly Val 215 220 Cys His Ile Tyr Val Asp Glu Ser Val Glu Ile Ala Glu Ala Leu Lys 230 235 Val Ile Val Asn Ala Lys Thr Gln Arg Pro Ser Thr Cys Asn Thr Val 250 Glu Thr Leu Leu Val Asn Lys Asn Ile Ala Asp Ser Phe Leu Pro Ala 265 Leu Ser Lys Gln Met Ala Glu Ser Gly Val Thr Leu His Ala Asp Ala 280 Ala Ala Leu Ala Gln Leu Gln Ala Gly Pro Ala Lys Val Val Ala Val 295 Lys Ala Glu Glu Tyr Asp Asp Glu Phe Leu Ser Leu Asp Leu Asn Val 315 310 Lys Ile Val Ser Asp Leu Asp Asp Ala Ile Ala His Ile Arg Glu His 330 Gly Thr Gln His Ser Asp Ala Ile Leu Thr Arg Asp Met Arg Asn Ala

<210> 359

<211> 186

<212> PRT

<213> Escherichia coli

<400> 359

 Met
 Met
 Thr
 Arg
 Gln
 Ala
 Ser
 Met
 Lys
 Gly
 Phe
 Pro
 Ile
 Ala
 His
 Ile

 Phe
 His
 Pro
 Ser
 Ile
 Pro
 Pro
 Pro
 His
 Ala
 Val
 Asn
 Asn
 Asn
 His
 Asn

 Arg
 Asn
 Ile
 Asp
 Tyr
 Trp
 Thr
 Val
 Lys
 Arg
 Lys
 Phe
 Ala
 Glu
 Ile
 Val

 Ser
 Thr
 Asn
 Asp
 Ile
 Thr
 Val
 Asp
 Ile
 Arg
 Ile
 Arg

100 105 110

Asp Val Gly Thr Phe Ala Pro Phe Gly Glu Gln Cys Thr Cys Ser Ala
115 120 125

Val Asn Lys Lys Glu Leu Glu Cys Ile Lys Glu Thr Ile Ser Lys Tyr

130 135 140
Cys Ala Lys Phe Thr Arg Lys Glu Ala Ile Leu Thr Pro Leu Val His

145 150 155 160
Phe Asn Lys Thr Ser Ile Thr Ser Asp Cys Trp Gln Ile Leu Phe Phe
165 170 175

Ser Pro Asp His Phe Asn Asn Asp Phe Tyr 180 185

<210> 360

<211> 395

<212> PRT

<213> Escherichia coli

<400> 360

 Met Phe Pro Val
 Ser Ser Ile Gly Asn Asp Ile Ser Ser Asp Leu Val

 1
 5

 Arg Arg Lys Met Asn Asp Leu Pro Glu Ser Pro Thr Gly Asn Asn Leu

 20
 25

 30

 Glu Ala Leu Ala Pro Gly Ile Glu Lys Leu Lys Gln Thr Ser Ile Glu

 35
 40

 Met Val Thr Leu Leu Asn Thr Leu Gln Pro Gly Gly Lys Cys Ile Ile

 50
 55

 60

 Thr Gly Asp Phe Gln Lys Glu Leu Ala Tyr Leu Gln Asn Val Ile Leu

 65
 70

 75
 80

 Tyr Asn Val Ser Ser Leu Arg Leu Asp Phe Leu Gly Tyr Asn Ala Gln

```
Ile Ile Gln Arg Ser Asp Asn Thr Cys Glu Leu Thr Ile Asn Glu Pro
                              105
Leu Lys Asn Gln Glu Ile Ser Thr Gly Asn Ile Asn Ile Asn Cys Pro
                           120
Leu Lys Asp Ile Tyr Asn Glu Ile Arg Arg Leu Asn Val Ile Phe Ser
                      135
                                         140
Cys Gly Thr Gly Asp Ile Val Asp Leu Ser Ser Leu Asp Leu Arg Asn
                  150
                                     155
Val Asp Leu Asp Tyr Tyr Asp Phe Thr Asp Lys His Met Ala Asn Thr
               165
                                  170
Ile Leu Asn Pro Phe Lys Leu Asn Ser Thr Asn Phe Thr Asn Ala Asn
                              185
Met Phe Gln Val Asn Phe Val Ser Ser Thr Gln Asn Ala Thr Ile Ser
                          200
                                      205
Trp Asp Tyr Leu Leu Lys Ile Thr Pro Val Leu Ile Ser Ile Ser Asp
                     215
                                          220
Met Tyr Ser Glu Glu Lys Ile Lys Phe Val Glu Ser Cys Leu Asn Glu
                  230
                                      235
Pro Gly Asp Ile Thr Glu Glu Gln Leu Lys Ile Met Arg Phe Ala Ile
               245
                                  250
Ile Lys Ser Ile Pro Arg Ala Thr Leu Thr Asp Lys Leu Glu Asn Glu
                              265
Leu Thr Lys Glu Ile Tyr Lys Ser Ser Ser Lys Ile Ile Asn Cys Leu
                          280
Asn Arg Ile Lys Leu Thr Glu Met Lys Glu Phe Ser Ser Glu Lys Ile
                       295
                                          300
Tyr Asp Tyr Ile Asp Ile Ile Ile Glu Asp Tyr Glu Asn Thr Lys Glu
                   310
                                       315
Asn Ala Tyr Leu Val Val Pro Gln Ile Asn Tyr Thr Met Asp Leu Asn
              325
                                  330
Ile Glu Asp Ser Ser Ser Glu Glu Leu Leu Ser Asp Asn Thr Leu Glu
           340
                              345
Lys Asp Glu Asn Ser Pro Asp Asn Gly Phe Glu Val Gly Glu Tyr Asn
                          360
                                              365
Thr Tyr Glu Ala Tyr Asn Ser Glu Lys Gln Tyr Phe Thr Arg Glu Asp
                    375
Tyr Thr Tyr Asp Tyr Asp Leu Leu Asn Ala Ile
                   390
385
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<210> 361

<211> 315

<212> PRT

<213> Escherichia coli

<400> 361

 Met
 Cys
 His
 Arg
 Ala
 Phe
 Arg
 Leu
 His
 Leu
 Cys
 Lys
 Asp
 Trp
 Val
 Phe

 Met
 Phe
 Ser
 Gly
 Leu
 Leu
 Ile
 Leu
 Val
 Pro
 Leu
 Ile
 Val
 Pro
 Leu
 Ile
 Tyr
 Jyr
 Jyr

Lys Leu Pro Ser Arg Ile Ala Met Ala Leu Glu Ser Leu Lys Leu Cys 120 Gly Val Val Ile Gly Phe Ala Ile Gly Leu Ser Gly Leu Ala Phe 135 Leu Gln His Ala Thr Glu Ala Ser Glu Tyr Thr Leu Ile Leu Leu 150 Phe Leu Val Gly Ile Gln Leu Arg Asn Asn Gly Met Thr Leu Lys Gln 165 170 Ile Val Leu Asn Arg Arg Gly Met Ile Val Ala Val Val Val Val 185 Ser Ser Leu Ile Gly Gly Leu Ile Asn Ala Phe Ile Leu Asp Leu Pro 200 Ile Asn Thr Ala Leu Ala Met Ala Ser Gly Phe Gly Trp Tyr Ser Leu 215 220 Ser Gly Ile Leu Leu Thr Glu Ser Phe Gly Pro Val Ile Gly Ser Ala 230 235 Ala Phe Phe Asn Asp Leu Ala Arg Glu Leu Ile Ala Ile Met Leu Ile 245 250 Pro Gly Leu Ile Arg Arg Ser Arg Ser Thr Ala Leu Gly Leu Cys Gly 260 265 Ala Thr Ser Met Asp Phe Thr Leu Pro Val Leu Gln Arg Thr Gly Gly 275 . 280 Leu Asp Met Val Pro Ala Ala Ile Val His Gly Phe Ile Leu Ser Leu 290 . 295 Leu Val Pro Ile Leu Ile Ala Phe Phe Ser Ala 310

<210> 362 <211> 96 <212> PRT

<213> Escherichia coli

## <400> 362

 Met Gln Asn Thr Thr His Asp Asn Val Ile Leu Glu Leu Thr Val Arg

 1
 5
 10
 15

 Asn His Pro Gly Val Met Thr His Val Cys Gly Leu Phe Ala Arg Arg
 30
 30

 Ala Phe Asn Val Glu Gly Ile Leu Cys Leu Pro Ile Gln Asp Ser Asp
 45

 Lys Ser His Ile Trp Leu Leu Val Asn Asp Asp Gln Arg Leu Glu Gln
 55
 60

 Met Ile Ser Gln Ile Asp Lys Leu Glu Asp Val Val Lys Val Gln Arg
 65
 70
 75
 80

 Asn Gln Ser Asp Pro Thr Met Phe Asn Lys Ile Ala Val Phe Phe Gln
 85
 90
 95

<210> 363 <211> 562 <212> PRT <213> Escherichia coli

<400> 363

 Met Ala Ser Ser Gly Thr Thr Ser Thr Arg Lys Arg Phe Thr Gly Ala

 1
 5
 10
 15

 Glu Phe Ile Val His Phe Leu Glu Gln Gln Gly Ile Lys Ile Val Thr
 20
 25
 30

 Gly Ile Pro Gly Gly Ser Ile Leu Pro Val Tyr Asp Ala Leu Ser Gln
 35
 40
 45

 Ser Thr Gln Ile Arg His Ile Leu Ala Arg His Glu Gln Gly Ala Gly

55 Phe Ile Ala Gln Gly Met Ala Arg Thr Asp Gly Lys Pro Ala Val Cys 70 75 Met Ala Cys Ser Gly Pro Gly Ala Thr Asn Leu Val Thr Ala Ile Ala 85 90 Asp Ala Arg Leu Asp Ser Ile Pro Leu Ile Cys Ile Thr Gly Gln Val 105 Pro Ala Ser Met Ile Gly Thr Asp Ala Phe Gln Glu Val Asp Thr Tyr 120 Gly Ile Ser Ile Pro Ile Thr Lys His Asn Tyr Leu Val Arg His Ile 135 140 Glu Glu Leu Pro Gln Val Met Ser Asp Ala Phe Arg Ile Ala Gln Ser 150 155 Gly Arg Pro Gly Pro Val Trp Ile Asp Ile Pro Lys Asp Val Gln Thr 165 170 Ala Val Phe Glu Ile Glu Thr Gln Pro Ala Met Ala Glu Lys Ala Ala 185 Ala Pro Ala Phe Ser Glu Glu Ser Ile Arg Asp Ala Ala Ala Met Ile 200 Asn Ala Ala Lys Arg Pro Val Leu Tyr Leu Gly Gly Val Ile Asn 215 220 Ala Pro Ala Arg Val Arg Glu Leu Ala Glu Lys Ala Gln Leu Pro Thr 230 235 Thr Met Thr Leu Met Ala Leu Gly Met Leu Pro Lys Ala His Pro Leu 245 250 Ser Leu Gly Met Leu Gly Met His Gly Val Arg Ser Thr Asn Tyr Ile 265 Leu Gln Glu Ala Asp Leu Leu Ile Val Leu Gly Ala Arg Phe Asp Asp 280 Arg Ala Ile Gly Lys Thr Glu Gln Phe Cys Pro Asn Ala Lys Ile Ile 295 His Val Asp Ile Asp Arg Ala Glu Leu Gly Lys Ile Lys Gln Pro His 310 315 Val Ala Ile Gln Ala Asp Val Asp Val Leu Ala Gln Leu Ile Pro 325 330 Leu Val Glu Ala Gln Pro Arg Ala Glu Trp His Gln Leu Val Ala Asp 340 345 Leu Gln Arg Glu Phe Pro Cys Pro Ile Pro Lys Ala Cys Asp Pro Leu 360 Ser His Tyr Gly Leu Ile Asn Ala Val Ala Ala Cys Val Asp Asn 375 380 Ala Ile Ile Thr Thr Asp Val Gly Gln His Gln Met Trp Thr Ala Gln 390 395 Ala Tyr Pro Leu Asn Arg Pro Arg Gln Trp Leu Thr Ser Gly Gly Leu 410 Gly Thr Met Gly Phe Gly Leu Pro Ala Ala Ile Gly Ala Ala Leu Ala 425 Asn Pro Asp Arg Lys Val Leu Cys Phe Ser Gly Asp Gly Ser Leu Met 440 Met Asn Ile Gln Glu Met Ala Thr Ala Ser Glu Asn Gln Leu Asp Val 455 Lys Ile Ile Leu Met Asn Asn Glu Ala Leu Gly Leu Val His Gln Gln 470 475 Gln Ser Leu Phe Tyr Glu Gln Gly Val Phe Ala Ala Thr Tyr Pro Gly 490 Lys Ile Asn Phe Met Gln Ile Ala Ala Gly Phe Gly Leu Glu Thr Cys 505 Asp Leu Asn Asn Glu Ala Asp Pro Gln Ala Ser Leu Gln Glu Ile Ile 520 Asn Arg Pro Gly Pro Ala Leu Ile His Val Arg Ile Asp Ala Glu Glu

Lys Val Tyr Pro Met Val Pro Pro Gly Ala Ala Asn Thr Glu Met Val 545 550 555 560 Gly Glu

<210> 364

<211> 32

<212> PRT

<213> Escherichia coli

<400> 364

Met Thr Thr Ser Met Leu Asn Ala Lys Leu Leu Pro Thr Ala Pro Ser

1 5 10 15

Ala Ala Val Val Val Val Arg Val Val Val Val Val Gly Asn Ala Pro
20 25 30

Met Phe Val Ile Trp Ser His Arg Thr Gly Phe Ile Met Ser His Gln

<210> 365

<211> 338

<212> PRT

<213> Escherichia coli

<400> 365

10 Leu Thr Phe Ala Asp Ser Glu Phe Ser Ser Lys Arg Arg Gln Thr Arg 25 Lys Glu Ile Phe Leu Ser Arg Met Glu Gln Ile Leu Pro Trp Gln Asn 40 Met Val Glu Val Ile Glu Pro Phe Tyr Pro Lys Ala Gly Asn Gly Arg 55 Arg Pro Tyr Pro Leu Glu Thr Met Leu Arg Ile His Cys Met Gln His 75 70 Trp Tyr Asn Leu Ser Asp Gly Ala Met Glu Asp Ala Leu Tyr Glu Ile 85 90 Ala Ser Met Arg Leu Phe Ala Arg Leu Ser Leu Asp Ser Ala Leu Pro 105 Asp Arg Thr Thr Ile Met Asn Phe Arg His Leu Leu Glu Gln His Gln 120 Leu Ala Arg Gln Leu Phe Lys Thr Ile Asn Arg Trp Leu Ala Glu Ala 135 Gly Val Met Met Thr Gln Gly Thr Leu Val Asp Ala Thr Ile Ile Glu 155 Ala Pro Ser Ser Thr Lys Asn Lys Glu Gln Gln Arg Asp Pro Glu Met 165 170 His Gln Thr Lys Lys Gly Asn Gln Trp His Phe Gly Met Lys Ala His 185 190 Ile Gly Val Asp Ala Lys Ser Gly Leu Thr His Ser Leu Val Thr Thr 200 . 205 Ala Ala Asn Glu His Asp Leu Asn Gln Leu Gly Asn Leu Leu His Gly 215 220 Glu Glu Gln Phe Val Ser Ala Asp Ala Gly Tyr Gln Gly Ala Pro Gln 235 . 240 . 230 Arg Glu Glu Leu Ala Glu Val Asp Val Asp Trp Leu Ile Ala Glu Arg 245 250 Pro Gly Lys Val Arg Thr Leu Lys Gln His Pro Arg Lys Asn Lys Thr 265 Ala Ile Asn Ile Glu Tyr Met Lys Ala Ser Ile Arg Ala Arg Val Glu 280 His Pro Phe Arg Ile Ile Lys Arg Gln Phe Gly Phe Val Lys Ala Arg

<210> 366 <211> 157 <212> PRT

<213> Escherichia coli

<400> 366

Met Val Tyr Ile Ile Val Ser His Gly His Glu Asp Tyr Ile Lys 10 Lys Leu Leu Glu Asn Leu Asn Ala Asp Asp Glu His Tyr Lys Ile Ile 20 25 Val Arg Asp Asn Lys Asp Ser Leu Leu Lys Gln Ile Cys Gln His 40 Tyr Ala Gly Leu Asp Tyr Ile Ser Gly Gly Val Tyr Gly Phe Gly His 55 Asn Asn Asn Ile Ala Val Ala Tyr Val Lys Glu Lys Tyr Arg Pro Ala 70 75 Asp Asp Asp Tyr Ile Leu Phe Leu Asn Pro Asp Ile Ile Met Lys His 85 90 Asp Asp Leu Leu Thr Tyr Ile Lys Tyr Val Glu Ser Lys Arg Tyr Ala 105 Phe Ser Thr Leu Cys Leu Phe Arg Asp Glu Ala Lys Ser Leu His Asp 115 120 125 Tyr Ser Val Arg Lys Phe Pro Val Leu Ser Asp Phe Ile Val Ser Phe 135 Met Leu Gly Ile Lys Glu Gly Ala Asn Lys Ser Leu Ile 150

<210> 367 <211> 372 <212> PRT <213> Escherichia coli

<400> 367

Met Gly Lys Ser Ile Val Val Val Ser Ala Val Asn Phe Thr Thr Gly Gly Pro Phe Thr Ile Leu Lys Lys Phe Leu Ala Ala Thr Asn Asn Lys 25 Glu Asn Val Ser Phe Ile Ala Leu Val His Ser Ala Lys Glu Leu Lys 40 Glu Ser Tyr Pro Trp Val Lys Phe Ile Glu Phe Pro Glu Val Lys Gly Ser Trp Leu Lys Arg Leu His Phe Glu Tyr Val Val Cys Lys Leu 75 Ser Lys Glu Leu Asn Ala Thr His Trp Ile Cys Leu His Asp Ile Thr 90 Ala Asn Val Val Thr Lys Lys Arg Tyr Val Tyr Cys His Asn Pro Ala 105 Pro Phe Tyr Lys Gly Ile Leu Phe Arg Glu Ile Leu Met Glu Pro Ser 120 125 Phe Phe Leu Phe Lys Met Leu Tyr Gly Leu Ile Tyr Lys Ile Asn Ile 130 135

```
Lys Lys Asn Thr Ala Val Phe Val Gln Gln Phe Trp Met Lys Glu Lys
                  150
Phe Ile Lys Lys Tyr Ser Ile Asn Asn Ile Ile Val Ser Arg Pro Glu
                                 170
Ile Lys Leu Ser Asp Lys Ser Gln Leu Thr Asp Asp Ser Gln Phe
                             185
Lys Asn Asn Pro Ser Glu Leu Thr Ile Phe Tyr Pro Ala Val Pro Arg
                          200
Val Phe Lys Asn Tyr Glu Leu Ile Ile Ser Ala Ala Arg Lys Leu Lys
                      215
                                         220
Glu Gln Ser Asn Ile Lys Phe Leu Leu Thr Ile Ser Gly Thr Glu Asn
                  230
                                     235
Ala Tyr Ala Lys Tyr Ile Ile Ser Leu Ala Glu Gly Leu Asp Asn Val
               245
                                 250
His Phe Leu Gly Tyr Leu Asp Lys Glu Lys Ile Asp His Cys Tyr Asn
                            265
                                                 270
Ile Ser Asp Ile Val Cys Phe Pro Ser Arg Leu Glu Thr Trp Gly Leu
                         280
Pro Leu Ser Glu Ala Lys Glu Arg Gly Lys Trp Val Leu Ala Ser Asp
                      295
                                        300
Phe Pro Phe Thr Arg Glu Thr Leu Gly Ser Tyr Glu Lys Lys Ala Phe
                  310
                                     315
Phe Asp Ser Asn Asn Asp Met Leu Val Lys Leu Ile Ile Asp Phe
            325
                     330 335
Lys Lys Gly Asn Leu Lys Lys Asp Ile Ser Asp Ala Asn Phe Ile Tyr
                             345
Arg Asn Glu Asn Val Leu Val Gly Phe Asp Glu Leu Val Asn Phe Ile
                         360
Thr Glu Glu His
   370
```

<210> 368 <211> 196 <212> PRT

<213> Escherichia coli

<400>, 368

Met Ile Leu Lys Leu Ala Lys Arg Tyr Gly Leu Cys Gly Phe Ile Arg 10 Leu Val Arg Asp Val Leu Leu Thr Arg Val Phe Tyr Arg Asn Cys Arg Ile Ile Arg Phe Pro Cys Tyr Ile Arg Asn Asp Gly Ser Ile Asn Phe 40 Gly Glu Asn Phe Thr Ser Gly Val Gly Leu Arg Leu Asp Ala Phe Gly 55 Arg Gly Val Ile Phe Phe Ser Asp Asn Val Gln Val Asn Asp Tyr Val 70 75 His Ile Ala Ser Ile Glu Ser Val Thr Ile Gly Arg Asp Thr Leu Ile 85 90 Ala Ser Lys Val Phe Ile Thr Asp His Asn His Gly Ser Phe Lys His 105 Ser Asp Pro Met Ser Ser Pro Asn Ile Pro Pro Asp Met Arg Thr Leu 120 Glu Ser Ser Ala Val Val Ile Gly Gln Arg Val Trp Leu Gly Glu Asn 135 140 Val Thr Val Leu Pro Gly Thr Ile Ile Gly Asn Gly Val Val Val Gly 150 155 Ala Asn Ser Val Val Arg Gly Ser Ile Pro Glu Asn Thr Val Ile Ala 170 Gly Val Pro Ala Lys Ile Ile Lys Lys Tyr Asn His Glu Thr Lys Leu

180 185 190 Trp Glu Lys Ala

195

<210> 369

<211> 330

<212> PRT

<213> Escherichia coli

<400> 369

Met Tyr Phe Leu Asn Asp Leu Asn Phe Ser Arg Asp Ala Gly Phe Lys Ala Arg Lys Asp Ala Leu Asp Ile Ala Ser Asp Tyr Glu Asn Ile Ser Val Val Asn Ile Pro Leu Trp Gly Gly Val Val Gln Arg Ile Ile 40 Ser Ser Val Lys Leu Ser Thr Phe Leu Cys Gly Leu Glu Asn Lys Asp 55 Val Leu Ile Phe Asn Phe Pro Met Ala Lys Pro Phe Trp His Ile Leu 70 75. Ser Phe Phe His Arg Leu Leu Lys Phe Arg Ile Val Pro Leu Ile His 90 Asp Ile Asp Glu Leu Arg Gly Gly Gly Ser Asp Ser Val Arg Leu 105 Ala Thr Cys Asp Met Val Ile Ser His Asn Pro Gln Met Thr Lys Tyr 120 Leu Ser Lys Tyr Met Ser Gln Asp Lys Ile Lys Asp Ile Lys Ile Phe 135 Asp Tyr Leu Val Ser Ser Asp Val Glu His Arg Asp Val Thr Asp Lys 150 155 Gln Arg Gly Val Ile Tyr Ala Gly Asn Leu Ser Arg His Lys Cys Ser 170 Phe Ile Tyr Thr Glu Gly Cys Asp Phe Thr Leu Phe Gly Val Asn Tyr 185 Glu Asn Lys Asp Asn Pro Lys Tyr Leu Gly Ser Phe Asp Ala Gln Ser 200 Pro Glu Lys Ile Asn Leu Pro Gly Met Gln Phe Gly Leu Ile Trp Asp 215 220 Gly Asp Ser Val Glu Thr Cys Ser Gly Ala Phe Gly Asp Tyr Leu Lys 230 235 Phe Asn Asn Pro His Lys Thr Ser Leu Tyr Leu Ser Met Glu Leu Pro 250 245 Val Phe Ile Trp Asp Lys Ala Ala Leu Ala Asp Phe Ile Val Asp Asn 265 Arg Ile Gly Tyr Ala Val Gly Ser Ile Lys Glu Met Gln Glu Ile Val 280 Asp Ser Met Thr Ile Glu Thr Tyr Lys Gln Ile Ser Glu Asn Thr Lys 295

Ile Ile Ser Gln Lys Ile Arg Thr Gly Ser Tyr Phe Arg Asp Val Leu

305 310 Glu Glu Val Ile Asp Asp Leu Lys Thr Arg 325 330

<210> 370

<211> 388

<212> PRT

<213> Escherichia coli

<400> 370

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Met Ile Tyr Leu Val Ile Ser Val Phe Leu Ile Thr Ala Phe Ile Cys
                                  10
Leu Tyr Leu Lys Lys Asp Ile Phe Tyr Pro Ala Val Cys Val Asn Ile
Ile Phe Ala Leu Val Leu Leu Gly Tyr Glu Ile Thr Ser Asp Ile Tyr
                           40
Ala Phe Gln Leu Asn Asp Ala Thr Leu Ile Phe Leu Leu Cys Asn Val
Leu Thr Phe Thr Leu Ser Cys Leu Leu Thr Glu Ser Val Leu Asp Leu
                  70
                                      75
Asn Ile Arg Lys Val Asn Asn Ala Ile Tyr Ser Ile Pro Ser Lys
              85
                                 90
Val His Asn Val Gly Leu Leu Val Ile Ser Phe Ser Met Ile Tyr Ile
                             105
                                                 110
Cys Met Arg Leu Ser Asn Tyr Gln Phe Gly Thr Ser Leu Leu Ser Tyr
                          120
                                             125
Met Asn Leu Ile Arg Asp Ala Asp Val Glu Asp Thr Ser Arg Asn Phe
                      135
Ser Ala Tyr Met Gln Pro Ile Ile Leu Thr Thr Phe Ala Leu Phe Ile
                  150
                                     155
Trp Ser Lys Lys Phe Thr Asn Thr Lys Val Ser Lys Thr Phe Thr Leu
              165
                               170
Leu Val Phe Ile Val Phe Ile Phe Ala Ile Ile Leu Asn Thr Gly Lys
                             185
Gln Ile Val Phe Met Val Ile Ile Ser Tyr Ala Phe Ile Val Gly Val
                          200
Asn Arg Val Lys His Tyr Val Tyr Leu Ile Thr Ala Val Gly Val Leu
                      215
Phe Ser Leu Tyr Met Leu Phe Leu Arg Gly Leu Pro Gly Gly Met Ala
       230
                                     235
Tyr Tyr Leu Ser Met Tyr Leu Val Ser Pro Ile Ile Ala Phe Gln Glu
                     250
           245
Phe Tyr Phe Gln Gln Val Ser Asn Ser Ala Ser Ser His Val Phe Trp
                             265
Phe Phe Glu Arg Leu Met Gly Leu Leu Thr Gly Gly Val Ser Met Ser
                          280
Leu His Lys Glu Phe Val Trp Val Gly Leu Pro Thr Asn Val Tyr Thr
                                         300
                      295
Ala Phe Ser Asp Tyr Val Tyr Ile Ser Ala Glu Leu Ser Tyr Leu Met
                  310
                                      315
Met Val Ile His Gly Cys Ile Ser Gly Val Leu Trp Arg Leu Ser Arg
               325
                      330
Asn Tyr Ile Ser Val Lys Ile Phe Tyr Ser Tyr Phe Ile Tyr Thr Phe
                              345
Ser Phe Ile Phe Tyr His Glu Ser Phe Met Thr Asn Ile Ser Ser Trp
                           360
Ile Gln Ile Thr Leu Cys Ile Ile Val Phe Ser Gln Phe Leu Lys Ala
                       375
Gln Lys Ile Lys
385
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<210> 371

<211> 367

<212> PRT

<213> Escherichia coli

<400> 371

Met Tyr Asp Tyr Ile Ile Val Gly Ser Gly Leu Phe Gly Ala Val Cys

1 10 15

Ala Asn Glu Leu Lys Lys Leu Asn Lys Lys Val Leu Val Ile Glu Lys

Arg Asn His Ile Gly Gly Asn Ala Tyr Thr Glu Asp Cys Glu Gly Ile 40 Gln Ile His Lys Tyr Gly Ala His Ile Phe His Thr Asn Asp Lys Tyr 55 Ile Trp Asp Tyr Val Asn Asp Leu Val Glu Phe Asn Arg Phe Thr Asn 70 75 Ser Pro Leu Ala Ile Tyr Lys Asp Lys Leu Phe Asn Leu Pro Phe Asn 85 90 Met Asn Thr Phe His Gln Met Trp Gly Val Lys Asp Pro Gln Glu Ala 105 Gln Asn Ile Ile Asn Ala Gln Lys Lys Lys Tyr Gly Asp Lys Val Pro 120 125 Glu Asn Leu Glu Glu Gln Ala Ile Ser Leu Val Gly Glu Asp Leu Tyr 135 140 Gln Ala Leu Ile Lys Gly Tyr Thr Glu Lys Gln Trp Gly Arg Ser Ala 150 155 Lys Glu Leu Pro Ala Phe Ile Ile Lys Arg Ile Pro Val Arg Phe Thr 170 165 Phe Asp Asn Asn Tyr Phe Ser Asp Arg Tyr Gln Gly Ile Pro Val Gly 185 Gly Tyr Thr Lys Leu Ile Glu Lys Met Leu Glu Gly Val Asp Val Lys 200 Leu Gly Ile Asp Phe Leu Lys Asp Lys Asp Ser Leu Ala Ser Lys Ala 215 220 His Arg Ile Ile Tyr Thr Gly Pro Ile Asp Gln Tyr Phe Asp Tyr Arg 230 235 Phe Gly Ala Leu Glu Tyr Arg Ser Leu Lys Phe Glu Thr Glu Arg His 245 250 Glu Phe Pro Asn Phe Gln Gly Asn Ala Val Ile Asn Phe Thr Asp Ala 260 265 Asn Val Pro Tyr Thr Arg Ile Ile Glu His Lys His Phe Asp Tyr Val 280 Glu Thr Lys His Thr Val Val Thr Lys Glu Tyr Pro Leu Glu Trp Lys 295 300 Val Gly Asp Glu Pro Tyr Tyr Pro Val Asn Asp Asn Lys Asn Met Glu 310 315 Leu Phe Lys Lys Tyr Arg Glu Leu Ala Ser Arg Glu Asp Lys Val Ile 325 330 Phe Gly Gly Arg Leu Ala Glu Tyr Lys Tyr Tyr Asp Met His Gln Val 345 Ile Ser Ala Ala Leu Tyr Gln Val Lys Asn Ile Met Ser Thr Asp

<210> 372

<211> 230

<212> PRT

<213> Escherichia coli

<400> 372

 Met Thr
 Ser Ser Ile
 Thr Asn Glu
 Ile Met Gln
 Leu Tyr Thr Asp Arg
 15

 Glu
 Val
 Leu Asn Met Gly
 Leu Cys Ser Arg Tyr Lys Ser Leu Thr Cys
 30
 30

 Asn
 Ser Cys Ser Met His Cys Gln
 Ile Met Pro Glu Glu Ser Pro Arg
 45

 Leu Gln
 Tyr Cys Ala Asn Ser Cys Phe Cys Met Trp Pro Glu Glu Glu Ser
 50

 Ser Tyr Phe Asn Arg Gly Val Val Glu Gly Ile Leu Thr Lys Asn His
 65

Asn Ala Arg Leu Ser Gly Tyr Ile Phe Val Asp Phe Ser Val Ser Phe 90 Leu Arg Leu Phe Leu Glu Lys Asp Trp Ile Asp Tyr Leu Ala Ser Thr 105 Asp Met Gly Ile Val Leu Val Ser Asp Arg Asn Met Gln Ser Leu Ala 120 115 125 Asn Tyr Trp Arg Lys His Asn Ser Ala Ile Ser Ala Val Ile Tyr Asn 135 140 Asp Asp Gly Leu Asp Val Ala Asn Glu Lys Ile Arg Gln Leu Phe Ile 150 155 Gly Arg Tyr Leu Ser Phe Thr Gly Gly Asn Thr Leu Thr Gln Met Glu 170 165 Phe Thr Ile Met Gly Tyr Met Val Ser Gly Tyr Asn Pro Tyr Gln Ile 185 Ala Glu Val Leu Asp Met Asp Ile Arg Ser Ile Tyr Ala Tyr Lys Gln 200 205 Arg Ile Glu Lys Arg Met Gly Gly Lys Ile Asn Glu Leu Phe Ile Arg 215 Ser His Ser Val Gln His . 230

<210> 373

<211> 391

<212> PRT

<213> Escherichia coli

<400> 373

Met Gln Lys Leu Ile Asn Ser Val Gln Asn Tyr Ala Trp Gly Ser Lys 10 Thr Ala Leu Thr Glu Leu Tyr Gly Met Glu Asn Pro Ser Ser Gln Pro 25 Met Ala Glu Leu Trp Met Gly Ala His Pro Lys Ser Ser Ser Arg Val 40 Gln Asn Ala Ala Gly Asp Ile Val Ser Leu Arg Asp Val Ile Glu Ser 55 Asp Lys Ser Thr Leu Leu Gly Glu Ala Val Ala Lys Arg Phe Gly Glu 70 · 75 Leu Pro Phe Leu Phe Lys Val Leu Cys Ala Ala Gln Pro Leu Ser Ile 85 90 Gln Val His Pro Asn Lys His Asn Ser Glu Ile Gly Phe Ala Lys Glu 100 105 Asn Ala Ala Gly Ile Pro Met Asp Ala Ala Glu Arg Asn Tyr Lys Asp 120 Pro Asn His Lys Pro Glu Leu Val Phe Ala Leu Thr Pro Phe Leu Ala 135 Met Asn Ala Phe Arg Glu Phe Ser Glu Ile Val Ser Leu Leu Gln Pro 150 155 Val Ala Gly Ala His Pro Ala Ile Ala His Phe Leu Gln Gln Pro Asp 165 170 Ala Glu Arg Leu Ser Glu Leu Phe Ala Ser Leu Leu Asn Met Gln Gly 185 Glu Glu Lys Ser Arg Ala Leu Ala Ile Leu Lys Ser Ala Leu Asp Ser . 200 Gln Gln Gly Glu Pro Trp Gln Thr Ile Arg Leu Ile Ser Glu Phe Tyr 215 Pro Glu Asp Ser Gly Leu Phe Ser Pro Leu Leu Leu Asn Val Val Lys 235 230 Leu Asn Pro Gly Glu Ala Met Phe Leu Phe Ala Glu Thr Pro His Ala 245 250 Tyr Leu Gln Gly Val Ala Leu Glu Val Met Ala Asn Ser Asp Asn Val

265 Leu Arg Ala Gly Leu Thr Pro Lys Tyr Ile Asp Ile Pro Glu Leu Val 280 Ala Asn Val Lys Phe Glu Ala Lys Pro Ala Asn Gln Leu Leu Thr Gln 295 Pro Val Lys Gln Gly Ala Glu Leu Asp Phe Pro Ile Pro Val Asp Asp 310 315 Phe Ala Phe Ser Leu His Asp Leu Ser Asp Lys Glu Thr Thr Ile Ser 325 330 Gln Gln Ser Ala Ala Ile Leu Phe Cys Val Glu Gly Asp Ala Thr Leu 345 Trp Lys Gly Ser Gln Gln Leu Gln Leu Lys Pro Gly Glu Ser Ala Phe 360 365 Ile Ala Ala Asn Glu Ser Pro Val Thr Val Lys Gly His Gly Arg Leu 375 Ala Arg Val Tyr Asn Lys Leu 390

<210> 374

<211> 264

<212> PRT

<213> Escherichia coli

260

<400> 374

Met Lys Gln Tyr Leu Glu Leu Met Gln Lys Val Leu Asp Glu Gly Thr Gln Lys Asn Asp Arg Thr Gly Thr Gly Thr Leu Ser Ile Phe Gly His 25 Gln Met Arg Phe Asn Leu Gln Asp Gly Phe Pro Leu Val Thr Thr Lys 40 Arg Cys His Leu Arg Ser Ile Ile His Glu Leu Leu Trp Phe Leu Gln 55 Gly Asp Thr Asn Ile Ala Tyr Leu His Glu Asn Asn Val Thr Ile Trp 70 75 Asp Glu Trp Ala Asp Glu Asn Gly Asp Leu Gly Pro Val Tyr Gly Lys 90 Gln Trp Arg Ala Trp Pro Thr Pro Asp Gly Arg His Ile Asp Gln Ile 105 Thr Thr Val Leu Asn Gln Leu Lys Asn Asp Pro Asp Ser Arg Arg Ile 120 Ile Val Ser Ala Trp Asn Val Gly Glu Leu Asp Lys Met Ala Leu Ala 135 140 Pro Cys His Ala Phe Phe Gln Phe Tyr Val Ala Asp Gly Lys Leu Ser 155 Cys Gln Leu Tyr Gln Arg Ser Cys Asp Val Phe Leu Gly Leu Pro Phe 170 Asn Ile Ala Ser Tyr Ala Leu Leu Val His Met Met Ala Gln Gln Cys 185 Asp Leu Glu Val Gly Asp Phe Val Trp Thr Gly Gly Asp Thr His Leu 200 Tyr Ser Asn His Met Asp Gln Thr His Leu Gln Leu Ser Arg Glu Pro 215 Arg Pro Leu Pro Lys Leu Ile Ile Lys Arg Lys Pro Glu Ser Ile Phe 230 235 Asp Tyr Arg Phe Glu Asp Phe Glu Ile Glu Gly Tyr Asp Pro His Pro 245 Gly Ile Lys Ala Pro Val Ala Ile

<210> 375 <211> 291 <212> PRT <213> Escherichia coli <400> 375 Met Thr Ser Ser Tyr Leu His Phe Pro Glu Phe Asp Pro Val Ile Phe Ser Ile Gly Pro Val Ala Leu His Trp Tyr Gly Leu Met Tyr Leu Val 20 Gly Phe Ile Phe Ala Met Trp Leu Ala Thr Arg Arg Ala Asn Arg Pro 40 Gly Ser Gly Trp Thr Lys Asn Glu Val Glu Asn Leu Leu Tyr Ala Gly. Phe Leu Gly Val Phe Leu Gly Gly Arg Ile Gly Tyr Val Leu Phe Tyr 70 75 Asn Phe Pro Gln Phe Met Ala Asp Pro Leu Tyr Leu Phe Arg Val Trp Asp Gly Gly Met Ser Phe His Gly Gly Leu Ile Gly Val Ile Val Val 100 105 Met Ile Ile Phe Ala Arg Arg Thr Lys Arg Ser Phe Phe Gln Val Ser 125 120 Asp Phe Ile Ala Pro Leu Ile Pro Phe Gly Leu Gly Ala Gly Arg Leu 135 140 Gly Asn Phe Ile Asn Gly Glu Leu Trp Gly Arg Val Asp Pro Asn Phe 145 150 155 Pro Phe Ala Met Leu Phe Pro Gly Ser Arg Thr Glu Asp Ile Leu Leu 165 170 Leu Gln Thr Asn Pro Gln Trp Gln Ser Ile Phe Asp Thr Tyr Gly Val 180 185 Leu Pro Arg His Pro Ser Gln Leu Tyr Glu Leu Leu Glu Gly Val 195 200 Val Leu Phe Ile Ile Leu Asn Leu Tyr Ile Arg Lys Pro Arg Pro Met 215 Gly Ala Val Ser Gly Leu Phe Leu Ile Gly Tyr Gly Ala Phe Arg Ile 230 235 Ile Val Glu Phe Phe Arg Gln Pro Asp Ala Gln Phe Thr Gly Ala Trp 250 Val Gln Tyr Ile Ser Met Gly Gln Ile Leu Ser Ile Pro Met Ile Val 265 . 270 Ala Gly Val Ile Met Met Val Trp Ala Tyr Arg Arg Ser Pro Gln Gln 280 His Val Ser 290 <210> 376 <211> 241 <212> PRT <213> Escherichia coli <400> 376 Met Asp Ser Leu Asn Leu Asn Lys His Ile Ser Gly Gln Phe Asn Ala 1 5 10 15 Glu Leu Glu Ser Ile Arg Thr Gln Val Met Thr Met Gly Gly Met Val 20 . 25 Glu Gln Gln Leu Ser Asp Ala Ile Thr Ala Met His Asn Gln Asp Ser 40 Asp Leu Ala Lys Arg Val Ile Glu Gly Asp Lys Asn Val Asn Met Met

Glu Val Ala Ile Asp Glu Ala Cys Val Arg Ile Ile Ala Lys Arg Gln

70 Pro Thr Ala Ser Asp Leu Arg Leu Val Met Val Ile Ser Lys Thr Ile 90 Ala Glu Leu Glu Arg Ile Gly Asp Val Ala Asp Lys Ile Cys Arg Thr 100 105 Ala Leu Glu Lys Phe Ser Gln Gln His Gln Pro Leu Leu Val Ser Leu 120 Glu Ser Leu Gly Arg His Thr Ile Gln Met Leu His Asp Val Leu Asp 135 Ala Phe Ala Arg Met Asp Ile Asp Glu Ala Val Arg Ile Tyr Arg Glu 150 155 Asp Lys Lys Val Asp Gln Glu Tyr Glu Gly Ile Val Arg Gln Leu Met 165 170 Thr Tyr Met Met Glu Asp Ser Arg Thr Ile Pro Ser Val Leu Thr Ala 180 185 Leu Phe Cys Ala Arg Ser Ile Glu Arg Ile Gly Asp Arg Cys Gln Asn 200 195 205 Ile Cys Glu Phe Ile Phe Tyr Tyr Val Lys Gly Gln Asp Phe Arg His 215 220 Val Gly Gly Asp Glu Leu Asp Lys Leu Leu Ala Gly Lys Asp Ser Asp 230 Lys

<210> 377

<211> 257

<212> PRT

<213> Escherichia coli

<400> 377

Met Ser Met Val Glu Thr Ala Pro Ser Lys Ile Gln Val Arg Asn Leu 10 Asn Phe Tyr Tyr Gly Lys Phe His Ala Leu Lys Asn Ile Asn Leu Asp 20 25 Ile Ala Lys Asn Gln Val Thr Ala Phe Ile Gly Pro Ser Gly Cys Gly 35 40 Lys Ser Thr Leu Leu Arg Thr Phe Asn Lys Met Phe Glu Leu Tyr Pro 55 Glu Gln Arg Ala Glu Gly Glu Ile Leu Leu Asp Gly Asp Asn Ile Leu 70 Thr Asn Ser Gln Asp Ile Ala Leu Leu Arg Ala Lys Val Gly Met Val 90 Phe Gln Lys Pro Thr Pro Phe Pro Met Ser Ile Tyr Asp Asn Ile Ala 105 Phe Gly Val Arg Leu Phe Glu Lys Leu Ser Arg Ala Asp Met Asp Glu 120 Arg Val Gln Trp Ala Leu Thr Lys Ala Ala Leu Trp Asn Glu Thr Lys 135 Asp Lys Leu His Gln Ser Gly Tyr Ser Leu Ser Gly Gly Gln Gln Gln 150 155 Arg Leu Cys Ile Ala Arg Gly Ile Ala Ile Arg Pro Glu Val Leu Leu 170 Leu Asp Glu Pro Cys Ser Ala Leu Asp Pro Ile Ser Thr Gly Arg Ile 185 Glu Glu Leu Ile Thr Glu Leu Lys Gln Asp Tyr Thr Val Val Ile Val 200 Thr His Asn Met Gln Gln Ala Ala Arg Cys Ser Asp His Thr Ala Phe 215 Met Tyr Leu Gly Glu Leu Ile Glu Phe Ser Asn Thr Asp Asp Leu Phe

Thr Lys Pro Ala Lys Lys Gln Thr Glu Asp Tyr Ile Thr Gly Arg Tyr
245 250 255

Gly

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<210> 378
<211> 296
<212> PRT
<213> Escherichia coli
<400> 378
Met Ala Met Val Glu Met Gln Thr Thr Ala Ala Leu Ala Glu Ser Arg
                            10
Arg Lys Met Gln Ala Arg Arg Leu Lys Asn Arg Ile Ala Leu Thr
                            25
Leu Ser Met Ala Thr Met Ala Phe Gly Leu Phe Trp Leu Ile Trp Ile
Leu Met Ser Thr Ile Thr Arg Gly Ile Asp Gly Met Ser Leu Ala Leu
                    55
Phe Thr Glu Met Thr Pro Pro Pro Asn Thr Glu Gly Gly Leu Ala
              70
Asn Ala Leu Ala Gly Ser Gly Leu Leu Ile Leu Trp Ala Thr Val Phe
                              90
           85
Gly Thr Pro Leu Gly Ile Met Ala Gly Ile Tyr Leu Ala Glu Tyr Gly
                           105
Arg Lys Ser Trp Leu Ala Glu Val Ile Arg Phe Ile Asn Asp Ile Leu
                        120
Leu Ser Ala Pro Ser Ile Val Val Gly Leu Phe Val Tyr Thr Ile Val
                    135
Val Ala Gln Met Glu His Phe Ser Gly Trp Ala Gly Val Ile Ala Leu
                 150
Ala Leu Leu Gln Val Pro Ile Val Ile Arg Thr Thr Glu Asn Met Leu
                              170
Lys Leu Val Pro Tyr Ser Leu Arg Glu Ala Ala Tyr Ala Leu Gly Thr
                          185
Pro Lys Trp Lys Met Ile Ser Ala Ile Thr Leu Lys Ala Ser Val Ser
     195 200
Gly Ile Met Thr Gly Ile Leu Leu Ala Ile Ala Arg Ile Ala Gly Glu
 210 . 215 220
Thr Ala Pro Leu Leu Phe Thr Ala Leu Ser Asn Gln Phe Trp Ser Thr
225 230 235 240
Asp Met Met Gln Pro Ile Ala Asn Leu Pro Val Thr Ile Phe Lys Phe
     245 250
Ala Met Ser Pro Phe Ala Glu Trp Gln Gln Leu Ala Trp Ala Gly Val
                           265
Leu Ile Ile Thr Leu Cys Val Leu Leu Leu Asn Ile Leu Ala Arg Val
                        280
Val Phe Ala Lys Asn Lys His Gly
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<210> 379

<211> 319

<212> PRT

<213> Escherichia coli

<400> 379

Met Ala Ala Thr Lys Pro Ala Phe Asn Pro Pro Gly Lys Lys Gly Asp 1 10 15 Ile Ile Phe Ser Val Leu Val Lys Leu Ala Ala Leu Ile Val Leu Leu

```
25
Met Leu Gly Gly Ile Ile Val Ser Leu Ile Ile Ser Ser Trp Pro Ser
                           40
Ile Gln Lys Phe Gly Leu Ala Phe Leu Trp Thr Lys Glu Trp Asp Ala
Pro Asn Asp Ile Tyr Gly Ala Leu Val Pro Ile Tyr Gly Thr Leu Val
Thr Ser Phe Ile Ala Leu Leu Ile Ala Val Pro Val Ser Phe Gly Ile
                                   90
Ala Leu Phe Leu Thr Glu Leu Ala Pro Gly Trp Leu Lys Arg Pro Leu
                               105
Gly Ile Ala Ile Glu Leu Leu Ala Ala Ile Pro Ser Ile Val Tyr Gly
                           120
Met Trp Gly Leu Phe Ile Phe Ala Pro Leu Phe Ala Val Tyr Phe Gln
                       135
Glu Pro Val Gly Asn Ile Met Ser Asn Ile Pro Ile Val Gly Ala Leu
                  150
                                       155
Phe Ser Gly Pro Ala Phe Gly Ile Gly Ile Leu Ala Ala Gly Val Ile
              165
                                  170
Leu Ala Ile Met Ile Ile Pro Tyr Ile Ala Ala Val Met Arg Asp Val
                              185
Phe Glu Gln Thr Pro Val Met Met Lys Glu Ser Ala Tyr Gly Ile Gly
                           200
                                               205
Cys Thr Thr Trp Glu Val Ile Trp Arg Ile Val Leu Pro Phe Thr Lys
                       215
                                          220
Asn Gly Val Ile Gly Gly Ile Met Leu Gly Leu Gly Arg Ala Leu Gly
                   230
                                       235
Glu Thr Met Ala Val Thr Phe Ile Ile Gly Asn Thr Tyr Gln Leu Asp
                                   250
Ser Ala Ser Leu Tyr Met Pro Gly Asn Ser Ile Thr Ser Ala Leu Ala
                               265
Asn Glu Phe Ala Glu Ala Glu Ser Gly Leu His Val Ala Ala Leu Met
                           280
Glu Leu Gly Leu Ile Leu Phe Val Ile Thr Phe Ile Val Leu Ala Ala
                       295
Ser Lys Phe Met Ile Met Arg Leu Ala Lys Asn Glu Gly Ala Arg
                  310
```

<210> 380

<211> 346

<212> PRT

<213> Escherichia coli

## <400> 380

 Met
 Lys
 Val
 Met
 Arg
 Thr
 Thr
 Val
 Ala
 Thr
 Val
 Ala
 Thr
 Val
 Ala
 Thr
 Val
 Ala
 Clu
 Ala
 Ala
 Thr
 Leu

 Ser
 Met
 Ser
 Ala
 Phe
 Ser
 Val
 Phe
 Ala
 Glu
 Ala
 Ser
 Lys
 Ala
 Ala
 Ser
 Ala
 Ala
 Phe
 Ala
 Glu
 Ala
 Ala

Tyr Leu Gly Lys Ile Lys Lys Trp Asp Asp Glu Ala Ile Ala Lys Leu 135 Asn Pro Gly Leu Lys Leu Pro Ser Gln Asn Ile Ala Val Val Arg Arg 155 150 Ala Asp Gly Ser Gly Thr Ser Phe Val Phe Thr Ser Tyr Leu Ala Lys 170 Val Asn Glu Glu Trp Lys Asn Asn Val Gly Thr Gly Ser Thr Val Lys 185 Trp Pro Ile Gly Leu Gly Gly Lys Gly Asn Asp Gly Ile Ala Ala Phe 200 Val Gln Arg Leu Pro Gly Ala Ile Gly Tyr Val Glu Tyr Ala Tyr Ala 215 220 Lys Gln Asn Asn Leu Ala Tyr Thr Lys Leu Ile Ser Ala Asp Gly Lys 230 235 Pro Val Ser Pro Thr Glu Glu Asn Phe Ala Asn Ala Ala Lys Gly Ala 245 250 Asp Trp Ser Lys Thr Phe Ala Gln Asp Leu Thr Asn Gln Lys Gly Glu 265 Asp Ala Trp Pro Ile Thr Ser Thr Thr Phe Ile Leu Ile His Lys Asp 275 280 285 Gln Lys Lys Pro Glu Gln Gly Thr Glu Val Leu Lys Phe Phe Asp Trp 295 300 Ala Tyr Lys Thr Gly Ala Lys Gln Ala Asn Asp Leu Asp Tyr Ala Ser 315 310 Leu Pro Asp Ser Val Val Glu Gln Val Arg Ala Ala Trp Lys Thr Asn 330 325 Ile Lys Asp Ser Ser Gly Lys Pro Leu Tyr 340

<210> 381

<211> 236

<212> PRT

<213> Escherichia coli

<400> 381

Met Gly Ser Gly Leu Val Asn Gly Gly Asp Tyr Phe Tyr Asn Asn Leu 10 Ser Phe Thr Val Thr Arg Tyr Asn Gly Ile Met Ala Thr Asp Ser Thr 25 Gln Cys Val Lys Lys Ser Arg Gly Arg Pro Lys Val Phe Asp Arg Asp 40 Ala Ala Leu Asp Lys Ala Met Lys Leu Phe Trp Gln His Gly Tyr Glu 55 Ala Thr Ser Leu Ala Asp Leu Val Glu Ala Thr Gly Ala Lys Ala Pro 70 75 Thr Leu Tyr Ala Glu Phe Thr Asn Lys Glu Gly Leu Phe Arg Ala Val 90 85 Leu Asp Arg Tyr Ile Asp Arg Phe Ala Ala Lys His Glu Ala Gln Leu 105 Phe Cys Glu Glu Lys Ser Val Glu Ser Ala Leu Ala Asp Tyr Phe Ala 120 ` . 125 Ala Ile Ala Asn Cys Phe Thr Ser Lys Asp Thr Pro Ala Gly Cys Phe . 135 Met Ile Asn Asn Cys Thr Thr Leu Ser Pro Asp Ser Gly Asp Ile Ala 155 150 Asn Thr Leu Lys Ser Arg His Ala Met Gln Glu Arg Thr Leu Gln Gln 170 Phe Leu Cys Gln Arg Gln Ala Arg Gly Glu Ile Pro Pro His Cys Asp 185 Val Thr His Leu Ala Glu Phe Leu Asn Cys Ile Ile Gln Gly Met Ser

200 Ile Ser Ala Arg Glu Gly Ala Ser Leu Glu Lys Leu Met Gln Ile Ala 215 Gly Thr Thr Leu Arg Leu Trp Pro Glu Leu Val Lys 230

<210> 382 <211> 181 <212> PRT <213> Escherichia coli

Met Gln Ala Lys Ile Ala Ala Ser Asn Thr Gly Glu Leu Asp Ala Leu Gln Gln Leu Gly Phe Ser Leu Val Glu Gly Glu Val Asp Leu Ala Leu 25 Pro Val Asn Asn Ala Ser Asp Ser Gly Ala Val Val Ala Gln Glu Thr 40 Asp Ile Pro Ala Leu Arg Gln Leu Ala Ser Ala Ala Phe Ala Gln Ser 55 60 Arg Phe Arg Ala Pro Trp Tyr Ala Pro Asp Ala Ser Ser Arg Phe Tyr 70 75 Ala Gln Trp Ile Glu Asn Ala Val Arg Gly Thr Phe Asp His Gln Cys 90 85 Leu Ile Leu Arg Ala Ala Ser Gly Asp Ile Arg Gly Tyr Val Ser Leu 105 Arg Glu Leu Asn Ala Thr Asp Ala Arg Ile Gly Leu Leu Ala Gly Arg 120 125 Gly Ala Gly Ala Glu Leu Met Gln Thr Ala Leu Asn Trp Ala Tyr Arg 135 140 Arg Gly Lys Thr Thr Leu Arg Val Ala Thr Gln Met Gly Asn Thr Ala 150 155 Ala Leu Lys Arg Tyr Ile Gln Ser Gly Ala Asn Val Glu Ser Thr Ala 165 170 Tyr Trp Leu Tyr Arg 180

<210> 383 <211> 376 <212> PRT <213> Escherichia coli

<400> 383

Met Ile Pro Phe Asn Ala Pro Pro Val Val Gly Thr Glu Leu Asp Tyr 10 Met Gln Ser Ala Met Gly Ser Gly Lys Leu Cys Gly Asp Gly Gly Phe 25 Thr Arg Arg Cys Gln Gln Trp Leu Glu Gln Arg Phe Gly Ser Ala Lys 40 Val Leu Leu Thr Pro Ser Cys Thr Ala Ser Leu Glu Met Ala Ala Leu 55 Leu Leu Asp Ile Gln Pro Gly Asp Glu Val Ile Met Pro Ser Tyr Thr 70 75 Phe Val Ser Thr Ala Asn Ala Phe Val Leu Arg Gly Ala Lys Ile Val 90 Phe Val Asp Val Arg Pro Asp Thr Met Asn Ile Asp Glu Thr Leu Ile 105 Glu Ala Ala Ile Thr Asp Lys Thr Arg Val Ile Val Pro Val His Tyr 120

Ala Gly Val Ala Cys Glu Met Asp Thr Ile Met Ala Leu Ala Lys Lys 135 140 His Asn Leu Phe Val Val Glu Asp Ala Ala Gln Gly Val Met Ser Thr 150 155 Tyr Lys Gly Arg Ala Leu Gly Thr Ile Gly His Ile Gly Cys Phe Ser 165 170 Phe His Glu Thr Lys Asn Tyr Thr Ala Gly Gly Glu Gly Gly Ala Thr 180 185 Leu Ile Asn Asp Lys Ala Leu Ile Glu Arg Ala Glu Ile Ile Arg Glu 200 Lys Gly Thr Asn Arg Ser Gln Phe Phe Arg Gly Gln Val Asp Lys Tyr 220 215 Thr Trp Arg Asp Ile Gly Ser Ser Tyr Leu Met Ser Asp Leu Gln Ala 230 235 Ala Tyr Leu Trp Ala Gln Leu Glu Ala Ala Asp Arg Ile Asn Gln Gln 245 250 Arg Leu Ala Leu Trp Gln Asn Tyr Tyr Asp Ala Leu Ala Pro Leu Ala 270 260 265 Lys Ala Gly Arg Ile Glu Leu Pro Ser Ile Pro Asp Gly Cys Val Gln 280 285 275 Asn Ala His Met Phe Tyr Ile Lys Leu Arg Asp Ile Asp Asp Arg Ser 295 300. Ala Leu Ile Asn Phe Leu Lys Glu Ala Glu Ile Met Ala Val Phe His 310 315 Tyr Ile Pro Leu His Gly Cys Pro Ala Gly Glu His Phe Gly Glu Phe 325 330 His Gly Glu Asp Arg Tyr Thr Thr Lys Glu Ser Glu Arg Leu Leu Arg 340 345 Leu Pro Leu Phe Tyr Asn Leu Ser Pro Val Asn Gln Arg Thr Val Ile 355 360 365 Ala Thr Leu Leu Asn Tyr Phe Ser 375

<210> 384

<211> 416

<212> PRT

<213> Escherichia coli

<400> 384

Met Ser Leu Ala Lys Ala Ser Leu Trp Thr Ala Ala Ser Thr Leu Val 10 Lys Ile Gly Ala Gly Leu Leu Val Gly Lys Leu Leu Ala Val Ser Phe 25 Gly Pro Ala Gly Leu Gly Leu Ala Ala Asn Phe Arg Gln Leu Ile Thr 40 Val Leu Gly Val Leu Ala Gly Ala Gly Ile Phe Asn Gly Val Thr Lys 55 Tyr Val Ala Gln Tyr His Asp Asn Pro Gln Gln Leu Arg Arg Val Val 75 70 Gly Thr Ser Ser Ala Met Val Leu Gly Phe Ser Thr Leu Met Ala Leu 90 Val Phe Val Leu Ala Ala Pro Ile Ser Gln Gly Leu Phe Gly Asn 105 Thr Asp Tyr Gln Gly Leu Val Arg Leu Val Ala Leu Val Gln Met Gly **120** . 125 Ile Ala Trp Gly Asn Leu Leu Leu Ala Leu Met Lys Gly Phe Arg Asp Ala Ala Gly Asn Ala Leu Ser Leu Ile Val Gly Ser Leu Ile Gly Val 155 Leu Ala Tyr Tyr Val Ser Tyr Arg Leu Gly Gly Tyr Glu Gly Ala Leu

```
165
                                   170
Leu Gly Leu Ala Leu Ile Pro Ala Leu Val Val Ile Pro Ala Ala Ile
                               185
Met Leu Ile Lys Arg Gly Val Ile Pro Leu Ser Tyr Leu Lys Pro Ser
                           200
Trp Asp Asn Gly Leu Ala Gly Gln Leu Ser Lys Phe Thr Leu Met Ala
                       215
                                           220
Leu Ile Thr Ser Val Thr Leu Pro Val Ala Tyr Ile Met Met Arg Lys
                   230
                                       235
Leu Leu Ala Ala Gln Tyr Ser Trp Asp Glu Val Gly Ile Trp Gln Gly
               245
                                   250
Val Ser Ser Ile Ser Asp Ala Tyr Leu Gln Phe Ile Thr Ala Ser Phe
                               265
Ser Val Tyr Leu Leu Pro Thr Leu Ser Arg Leu Thr Glu Lys Arg Asp
                           280
Ile Thr Arg Glu Val Val Lys Ser Leu Lys Phe Val Leu Pro Ala Val
                       295
Ala Ala Ala Ser Phe Thr Val Trp Leu Leu Arg Asp Phe Ala Ile Trp
                   310
                                        315
Leu Leu Leu Ser Asn Lys Phe Thr Ala Met Arg Asp Leu Phe Ala Trp
                                    330
Gln Leu Val Gly Asp Val Leu Lys Val Gly Ala Tyr Val Phe Gly Tyr
                               345
Leu Val Ile Ala Lys Ala Ser Leu Arg Phe Tyr Ile Leu Ala Glu Val
                            360
Ser Gln Phe Thr Leu Leu Met Val Phe Ala His Trp Leu Ile Pro Ala
                        375
                                           380
His Gly Ala Leu Gly Ala Ala Gln Ala Tyr Met Ala Thr Tyr Ile Val
                   390
                                       395
Tyr Phe Ser Leu Cys Cys Gly Val Phe Leu Leu Trp Arg Arg Ala
                405
                                    410
```

<210> 385

<211> 450

<212> PRT

<213> Escherichia coli

<400> 385

Met Ser Leu Leu Gln Phe Ser Gly Leu Phe Val Val Trp Leu Leu Cys 10 Thr Leu Phe Ile Ala Thr Leu Thr Trp Phe Glu Phe Arg Arg Val Arg 25 Phe Asn Phe Asn Val Phe Phe Ser Leu Leu Phe Leu Leu Thr Phe Phe 40 Phe Gly Phe Pro Leu Thr Ser Val Leu Val Phe Arg Phe Asp Val Gly 55 Val Ala Pro Pro Glu Ile Leu Leu Gln Ala Leu Leu Ser Ala Gly Cys 75 70 Phe Tyr Ala Val Tyr Tyr Val Thr Tyr Lys Thr Arg Leu Arg Lys Arg 90 Val Ala Asp Val Pro Arg Arg Pro Leu Phe Thr Met Asn Arg Val Glu 105 Thr Asn Leu Thr Trp Val Ile Leu Met Gly Ile Ala Leu Val Ser Val 120 125 Gly Ile Phe Phe Met His Asn Gly Phe Leu Leu Phe Arg Leu Asn Ser 140 135 Tyr Ser Gln Ile Phe Ser Ser Glu Val Ser Gly Val Ala Leu Lys Arg 150 155 Phe Phe Tyr Phe Phe Ile Pro Ala Met Leu Val Val Tyr Phe Leu Arg 170 165

```
Gln Asp Ser Lys Ala Trp Leu Phe Phe Leu Val Ser Thr Val Ala Phe
                              185
Gly Leu Leu Thr Tyr Met Ile Val Gly Gly Thr Arg Ala Asn Ile Ile
                          200
Ile Ala Phe Ala Ile Phe Leu Phe Ile Gly Ile Ile Arg Gly Trp Ile
                      215
Ser Leu Trp Met Leu Ala Ala Gly Val Leu Gly Ile Val Gly Met
                                      235
Phe Trp Leu Ala Leu Lys Arg Tyr Gly Met Asn Val Ser Gly Asp Glu
                                 250
Ala Phe Tyr Thr Phe Leu Tyr Leu Thr Arg Asp Thr Phe Ser Pro Trp
                              265
Glu Asn Leu Ala Leu Leu Gln Asn Tyr Asp Asn Ile Asp Phe Gln
                         280
Gly Leu Ala Pro Ile Val Arg Asp Phe Tyr Val Phe Ile Pro Ser Trp
                      295
                                         300
Leu Trp Pro Gly Arg Pro Ser Met Val Leu Asn Ser Ala Asn Tyr Phe
                                     315
                  310
Thr Trp Glu Val Leu Asn Asn His Ser Gly Leu Ala Ile Ser Pro Thr
                                  330 ·
Leu Ile Gly Ser Leu Val Val Met Gly Gly Ala Leu Phe Ile Pro Leu
                             345
Gly Ala Ile Val Val Gly Leu Ile Ile Lys Trp Phe Asp Trp Leu Tyr
                                             365
                      360
Glu Leu Gly Asn Arg Glu Pro Asn Arg Tyr Lys Ala Ala Ile Leu His
                  375
                                         380
Ser Phe Cys Phe Gly Ala Ile Phe Asn Met Ile Val Leu Ala Arg Glu
                           395
                   390
Gly Leu Asp Ser Phe Val Ser Arg Val Val Phe Phe Ile Val Val Phe
              405
                                 410
Gly Ala Cys Leu Met Ile Ala Lys Leu Leu Tyr Trp Leu Phe Glu Ser
                                              430
                              425
Ala Gly Leu Ile His Lys Arg Thr Lys Ser Ser Leu Arg Thr Gln Val
                         440
Glu Gly
  450
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<210> 386

<211> 246

<212> PRT

<213> Escherichia coli

## <400> 386

Met Asn Asn Asn Thr Thr Ala Pro Thr Tyr Thr Leu Arg Gly Leu Gln 10 Leu Ile Gly Trp Arg Asp Met Gln His Ala Leu Asp Tyr Leu Phe Ala 25 Asp Gly Gln Leu Lys Gln Gly Thr Leu Val Ala Ile Asn Ala Glu Lys 40 Met Leu Thr Ile Glu Asp Asn Ala Glu Val Arg Glu Leu Ile Asn Ala 55 Ala Glu Phe Lys Tyr Ala Asp Gly Ile Ser Val Val Arg Ser Val Arg 75 70 Lys Lys Tyr Pro Gln Ala Gln Val Ser Arg Val Ala Gly Ala Asp Leu 85 Trp Glu Glu Leu Met Ala Arg Ala Gly Lys Glu Gly Thr Pro Val Phe 105 Leu Val Gly Gly Lys Pro Glu Val Leu Ala Gln Thr Glu Ala Lys Leu 120

Arg Asn Gln Trp Asn Val Asn Ile Val Gly Ser Gln Asp Gly Tyr Phe

135 140 Lys Pro Glu Gln Arg Gln Ala Leu Phe Glu Arg Ile His Ala Ser Gly 150 155 Ala Gln Ile Val Thr Val Ala Met Gly Ser Pro Lys Gln Glu Ile Ile 165 170 Met Arg Asp Cys Arg Leu Val His Pro Asp Ala Leu Tyr Met Gly Val 185 Gly Gly Thr Tyr Asp Val Phe Thr Gly His Val Lys Arg Ala Pro Lys 200 Ile Trp Gln Thr Leu Gly Leu Glu Trp Leu Tyr Arg Leu Leu Ser Gln 215 220 Pro Ser Arq Ile Lys Arq Gln Leu Arq Leu Leu Arq Tyr Leu Arq Trp 230 235 His Tyr Thr Gly Asn Leu 245

<210> 387

<211> 74

<212> PRT

<213> Escherichia coli

<400> 387

 Met Thr Val Leu Ile His Val Leu Gly Ser Asp Ile Pro His His Asn 1
 5
 10
 15

 Arg Thr Val Leu Arg Phe Phe Asn Asp Ala Leu Ala Ala Thr Ser Glu 20
 25
 30

 His Ala Arg Glu Phe Met Val Val Gly Lys Asp Asp Gly Leu Ser Asp 35
 40
 45

 Ser Cys Pro Ala Leu Ser Val Gln Phe Phe Pro Trp Glu Lys Ile Ala 50
 55
 60

 Gly Gly Ser Gly His Arg Glu Ser Lys Ser 65
 70

<210> 388

<211> 204

<212> PRT

<213> Escherichia coli

<400> 388

Met Arg Gly Glu Leu Leu Phe Phe Pro Thr Arg Met Asp Pro Ser Leu 5 · 10 Asn Thr Met Ala Asn Asp Arg Gln Arg Glu Gly Lys Met Thr Ile Leu 25 Val Gly Asn Ser Gly Asp Arg Ser Asn Glu His Ile Ala Ala Leu Arg 40 Ala Val His Gln Gln Phe Gly Asp Thr Val Lys Val Val Val Pro Met 55 Gly Tyr Pro Pro Asn Asn Glu Ala Tyr Ile Glu Glu Val Arg Gln Ala 70 75 Gly Leu Glu Leu Phe Ser Glu Glu Asn Leu Gln Ile Leu Ser Glu Lys 90 Leu Glu Phe Asp Ala Tyr Leu Ala Leu Leu Arg Gln Cys Asp Leu Gly 100 105 Tyr Phe Ile Phe Ala Arg Gln Gln Gly Ile Gly Thr Leu Cys Leu Leu 120 Ile Gln Ala Gly Ile Pro Cys Val Leu Asn Arg Glu Asn Pro Phe Trp 135 140 Gln Asp Met Thr Glu Gln His Leu Pro Val Leu Phe Thr Thr Asp Asp 150

Leu Asn Glu Asp Ile Val Arg Glu Ala Gln Arg Gln Leu Ala Ser Val
165 170 175

Asp Lys Asn Thr Ile Ala Phe Phe Ser Pro Asn Tyr Leu Gln Gly Trp
180 185 190

Gln Arg Ala Leu Ala Ile Ala Ala Arg Glu Val Ala
195 200

<210> 389

<210> 389 <211> 182 <212> PRT <213> Escherichia coli

<400> 389 Met Ile Arg Gln Arg Arg Ala Leu Thr Pro Glu Gln Gln Glu Met Gly Gln Gln Ala Ala Thr Arg Met Met Thr Tyr Pro Pro Val Val 25 Met Ala His Thr Val Ala Val Phe Leu Ser Phe Asp Gly Glu Leu Asp 40 Thr Gln Pro Leu Ile Glu Gln Leu Trp Arg Ala Gly Lys Arg Val Tyr 55 Leu Pro Val Leu His Pro Phe Ser Ala Gly Asn Leu Leu Phe Leu Asn Tyr His Pro Gln Ser Glu Leu Val Met Asn Arg Leu Lys Ile His Glu 90 Pro Lys Leu Asp Val Arg Asp Val Leu Pro Leu Ser Arg Leu Asp Val 105 100 Leu Ile Thr Pro Leu Val Ala Phe Asp Glu Tyr Gly Gln Arg Leu Gly 120 125 Met Gly Gly Gly Phe Tyr Asp Arg Thr Leu Gln Asn Trp Gln His Tyr 135 Lys Thr Gln Pro Val Gly Tyr Ala His Asp Cys Gln Leu Val Glu Lys 150 155 Leu Pro Val Glu Glu Trp Asp Ile Pro Leu Pro Ala Val Val Thr Pro 165 170 Ser Lys Val Trp Glu Trp 180

<210> 390 <211> 91 <212> PRT <213> Escherichia coli

<400> 390 Met Ala Arg Val Thr Val Gln Asp Ala Val Glu Lys Ile Gly Asn Arg 10 Phe Asp Leu Val Leu Val Ala Ala Arg Arg Ala Arg Gln Met Gln Val 25 Gly Gly Lys Asp Pro Leu Val Pro Glu Glu Asn Asp Lys Thr Thr Val 45 40 Ile Ala Leu Arg Glu Ile Glu Glu Gly Leu Ile Asn Asn Gln Ile Leu 60 55 Asp Val Arg Glu Arg Gln Glu Gln Glu Gln Glu Ala Ala Glu Leu 75 80 70 Gln Ala Val Thr Ala Ile Ala Glu Gly Arg Arg 85

<210> 391

<211> 702

<212> PRT

<213> Escherichia coli

<400> 391

Met Tyr Leu Phe Glu Ser Leu Asn Gln Leu Ile Gln Thr Tyr Leu Pro Glu Asp Gln Ile Lys Arg Leu Arg Gln Ala Tyr Leu Val Ala Arg Asp 25 Ala His Glu Gly Gln Thr Arg Ser Ser Gly Glu Pro Tyr Ile Thr His 40 Pro Val Ala Val Ala Cys Ile Leu Ala Glu Met Lys Leu Asp Tyr Glu 55 Thr Leu Met Ala Ala Leu Leu His Asp Val Ile Glu Asp Thr Pro Ala Thr Tyr Gln Asp Met Glu Gln Leu Phe Gly Lys Ser Val Ala Glu Leu 90 Val Glu Gly Val Ser Lys Leu Asp Lys Leu Lys Phe Arg Asp Lys Lys 100 105 Glu Ala Gln Ala Glu Asn Phe Arg Lys Met Ile Met Ala Met Val Gln 120 125 Asp Ile Arg Val Ile Leu Ile Lys Leu Ala Asp Arg Thr His Asn Met 135 Arg Thr Leu Gly Ser Leu Arg Pro Asp Lys Arg Arg Arg Ile Ala Arg 155 150 Glu Thr Leu Glu Ile Tyr Ser Pro Leu Ala His Arg Leu Gly Ile His 165 170 His Ile Lys Thr Glu Leu Glu Glu Leu Gly Phe Glu Ala Leu Tyr Pro 185 180 Asn Arg Tyr Arg Val Ile Lys Glu Val Val Lys Ala Ala Arg Gly Asn 200 Arg Lys Glu Met Ile Gln Lys Ile Leu Ser Glu Ile Glu Gly Arg Leu 215 Gln Glu Ala Gly Ile Pro Cys Arg Val Ser Gly Arg Glu Lys His Leu 230 235 Tyr Ser Ile Tyr Cys Lys Met Val Leu Lys Glu Gln Arg Phe His Ser 250 Ile Met Asp Ile Tyr Ala Phe Arg Val Ile Val Asn Asp Ser Asp Thr 265 Cys Tyr Arg Val Leu Gly Gln Met His Ser Leu Tyr Lys Pro Arg Pro 280 Gly Arg Val Lys Asp Tyr Ile Ala Ile Pro Lys Ala Asn Gly Tyr Gln 295 300 Ser Leu His Thr Ser Met Ile Gly Pro His Gly Val Pro Val Glu Val 315 310 Gln Ile Arg Thr Glu Asp Met Asp Gln Met Ala Glu Met Gly Val Ala 330 325 Ala His Trp Ala Tyr Lys Glu His Gly Glu Thr Ser Thr Thr Ala Gln 345 Ile Arg Ala Gln Arg Trp Met Gln Ser Leu Leu Glu Leu Gln Gln Ser 360 Ala Gly Ser Ser Phe Glu Phe Ile Glu Ser Val Lys Ser Asp Leu Phe 380 375 Pro Asp Glu Ile Tyr Val Phe Thr Pro Glu Gly Arg Ile Val Glu Leu 395 390 Pro Ala Gly Ala Thr Pro Val Asp Phe Ala Tyr Ala Val His Thr Asp 410 Ile Gly His Ala Cys Val Gly Ala Arg Val Asp Arg Gln Pro Tyr Pro 425 Leu Ser Gln Pro Leu Thr Ser Gly Gln Thr Val Glu Ile Ile Thr Ala 440

```
Pro Gly Ala Arg Pro Asn Ala Ala Trp Leu Asn Phe Val Val Ser Ser
              455
Lys Ala Arg Ala Lys Ile Arg Gln Leu Leu Lys Asn Leu Lys Arg Asp
                                475
               470
Asp Ser Val Ser Leu Gly Arg Arg Leu Leu Asn His Ala Leu Gly Gly
             485
                             490
Ser Arg Lys Leu Asn Glu Ile Pro Gln Glu Asn Ile Gln Arg Glu Leu
         500 505
Asp Arg Met Lys Leu Ala Thr Leu Asp Asp Leu Leu Ala Glu Ile Gly
             520
Leu Gly Asn Ala Met Ser Val Val Val Ala Lys Asn Leu Gln His Gly
       535
                                     540
Asp Ala Ser Ile Pro Pro Ala Thr Gln Ser His Gly His Leu Pro Ile
                                 555
   550
Lys Gly Ala Asp Gly Val Leu Ile Thr Phe Ala Lys Cys Cys Arg Pro
                             570
            565
Ile Pro Gly Asp Pro Ile Ile Ala His Val Ser Pro Gly Lys Gly Leu
                          585
         580
Val Ile His His Glu Ser Cys Arg Asn Ile Arg Gly Tyr Gln Lys Glu
     595 . 600
Pro Glu Lys Phe Met Ala Val Glu Trp Asp Lys Glu Thr Ala Gln Glu
                                     620
        615
Phe Ile Thr Glu Ile Lys Val Glu Met Phe Asn His Gln Gly Ala Leu
                                 635
       630
Ala Asn Leu Thr Ala Ala Ile Asn Thr Thr Thr Ser Asn Ile Gln Ser
                 650
          645
Leu Asn Thr Glu Glu Lys Asp Gly Arg Val Tyr Ser Ala Phe Ile Arg
                          665
       660
Leu Thr Ala Arg Asp Arg Val His Leu Ala Asn Ile Met Arg Lys Ile
                       680
Arg Val Met Pro Asp Val Ile Lys Val Thr Arg Asn Arg Asn
                   695
```

<210> 392

<211> 229

<212> PRT

<213> Escherichia coli

<400> 392

Met Asn Pro Thr Arg Tyr Ala Arg Ile Cys Glu Met Leu Ala Arg Arg 10 Gln Pro Asp Leu Thr Val Cys Met Glu Gln Val His Lys Pro His Asn 25 Val Ser Ala Ile Ile Arg Thr Ala Asp Ala Val Gly Val His Glu Val 40 His Ala Val Trp Pro Gly Ser Arg Met Arg Thr Met Ala Ser Ala Ala 55 Ala Gly Ser Asn Ser Trp Val Gln Val Lys Thr His Arg Thr Ile Gly 70 Asp Ala Val Ala His Leu Lys Gly Gln Gly Met Gln Ile Leu Ala Thr .90 · 95 85 . . His Leu Ser Asp Asn Ala Val Asp Phe Arg Glu Ile Asp Tyr Thr Arg 105 Pro Thr Cys Ile Leu Met Gly Gln Glu Lys Thr Gly Ile Thr Gln Glu 120 115 Ala Leu Ala Leu Ala Asp Gln Asp Ile Ile Ile Pro Met Ile Gly Met 135 Val Gln Ser Leu Asn Val Ser Val Ala Ser Ala Leu Ile Leu Tyr Glu 155 150 Ala Gln Arg Gln Arg Gln Asn Ala Gly Met Tyr Leu Arg Glu Asn Ser

Val Gly Ala Ala Leu Ser Asn Lys Leu Ala Lys Ile Asn Leu His Thr Val Gln Asp Leu Leu His Leu Pro Leu Arg Tyr Glu Asp Arg Thr 40 His Leu Tyr Pro Ile Gly Glu Leu Leu Pro Gly Val Tyr Ala Thr Val 55 Glu Gly Glu Val Leu Asn Cys Asn Ile Ser Phe Gly Gly Arg Arg Met 70 75 Met Thr Cys Gln Ile Ser Asp Gly Ser Gly Ile Leu Thr Met Arg Phe 90 Phe Asn Phe Ser Ala Ala Met Lys Asn Ser Leu Ala Ala Gly Arg Arg 100 105 Val Leu Ala Tyr Gly Glu Ala Lys Arg Gly Lys Tyr Gly Ala Glu Met 120 Ile His Pro Glu Tyr Arg Val Gln Gly Asp Leu Ser Thr Pro Glu Leu 135 Gln Glu Thr Leu Thr Pro Val Tyr Pro Thr Thr Glu Gly Val Lys Gln 150 155 Ala Thr Leu Arg Lys Leu Thr Asp Gln Ala Leu Asp Leu Leu Asp Thr 165 170 Cys Ala Ile Glu Glu Leu Leu Pro Pro Glu Leu Ser Gln Gly Met Met 185 180 Thr Leu Pro Glu Ala Leu Arg Thr Leu His Arg Pro Pro Pro Thr Leu 200 Gln Leu Ser Asp Leu Glu Thr Gly Gln His Pro Ala Gln Arg Arg Leu 215 220 Ile Leu Glu Glu Leu Leu Ala His Asn Leu Ser Met Leu Ala Leu Arg 235 230 Ala Gly Ala Gln Arg Phe His Ala Gln Pro Leu Ser Ala Asn Asp Thr 250 245 Leu Lys Asn Lys Leu Leu Ala Ala Leu Pro Phe Lys Pro Thr Gly Ala 265 Gln Ala Arg Val Val Ala Glu Ile Glu Arg Asp Met Ala Leu Asp Val 280 Pro Met Met Arg Leu Val Gln Gly Asp Val Gly Ser Gly Lys Thr Leu 295 300 Val Ala Ala Leu Ala Leu Arg Ala Ile Ala His Gly Lys Gln Val 310 315 Ala Leu Met Ala Pro Thr Glu Leu Leu Ala Glu Gln His Ala Asn Asn 330 325 Phe Arg Asn Trp Phe Ala Pro Leu Gly Ile Glu Val Gly Trp Leu Ala

-402-

345

340

```
Gly Lys Gln Lys Gly Lys Ala Arg Leu Ala Gln Gln Glu Ala Ile Ala
                          360
Ser Gly Gln Val Gln Met Ile Val Gly Thr His Ala Ile Phe Gln Glu
                      375
Gln Val Gln Phe Asn Gly Leu Ala Leu Val Ile Ile Asp Glu Gln His
                  390
                                      395 .
Arg Phe Gly Val His Gln Arg Leu Ala Leu Trp Glu Lys Gly Gln Gln
                                  410
Gln Gly Phe His Pro His Gln Leu Ile Met Thr Ala Thr Pro Ile Pro
                              425
Arg Thr Leu Ala Met Thr Ala Tyr Ala Asp Leu Asp Thr Ser Val Ile
                           440
Asp Glu Leu Pro Pro Gly Arg Thr Pro Val Thr Thr Val Ala Ile Pro
Asp Thr Arg Arg Thr Asp Ile Ile Asp Arg Val His His Ala Cys Ile
                  470
                                     475
Thr Glu Gly Arg Gln Ala Tyr Trp Val Cys Thr Leu Ile Glu Glu Ser
                                  490
              485
Glu Leu Leu Glu Ala Gln Ala Ala Glu Ala Thr Trp Glu Glu Leu Lys
                              505
          500
Leu Ala Leu Pro Glu Leu Asn Val Gly Leu Val His Gly Arg Met Lys
                          520
                                              525
Pro Ala Glu Lys Gln Ala Val Met Ala Ser Phe Lys Gln Gly Glu Leu
                      535
                                         540 .
His Leu Leu Val Ala Thr Thr Val Ile Glu Val Gly Val Asp Val Pro
                   550
                                      555
Asn Ala Ser Leu Met Ile Ile Glu Asn Pro Glu Arg Leu Gly Leu Ala
                                  570
            565
Gln Leu His Gln Leu Arg Gly Arg Val Gly Arg Gly Ala Val Ala Ser
                               585
His Cys Val Leu Leu Tyr Lys Thr Pro Leu Ser Lys Thr Ala Gln Ile
                          600
Arg Leu Gln Val Leu Arg Asp Ser Asn Asp Gly Phe Val Ile Ala Gln
                       615
                                           620
Lys Asp Leu Glu Ile Arg Gly Pro Gly Glu Leu Leu Gly Thr Arg Gln
                  630
                                      635
Thr Gly Asn Ala Glu Phe Lys Val Ala Asp Leu Leu Arg Asp Gln Ala
                       . 650
Met Ile Pro Glu Val Gln Arg Leu Ala Arg His Ile His Glu Arg Tyr
                               665
Pro Gln Gln Ala Lys Ala Leu Ile Glu Arg Trp Met Pro Glu Thr Glu
Arg Tyr Ser Asn Ala
    690
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<210> 394

<211> 428

<212> PRT

<213> Escherichia coli

<400> 394

 Met
 Lys
 Thr
 Ser
 Leu
 Phe
 Lys
 Ser
 Leu
 Tyr
 Phe
 Gln
 Val
 Leu
 Thr
 Ala

 1le
 Ala
 Ile
 Gly
 Ile
 Leu
 Leu
 Gly
 His
 Phe
 Tyr
 Pro
 Glu
 Ile
 Gly
 Glu

 Gln
 Met
 Lys
 Pro
 Leu
 Gly
 Asp
 Gly
 Phe
 Val
 Lys
 Leu
 Ile
 Lys
 Met
 Ile

 Jle
 Ala
 Pro
 Val
 Ile
 Phe
 Cys
 Thr
 Val
 Val
 Thr
 Gly
 Ile
 Ala
 Gly
 Met

 Jle
 Ala
 Ile
 Phe
 Cys
 Thr
 Val
 Val
 Thr
 Gly
 Ile
 Ala
 Gly
 Met

 Jle
 Ala
 Ile
 Phe
 Cys
 Thr
 Val
 Thr
 Gly
 Ala
 Val
 Ile
 Ala
 Leu
 Leu
 Tyr

```
70
Phe Glu Ile Val Ser Thr Ile Ala Leu Ile Ile Gly Leu Ile Ile Val
Asn Val Val Gln Pro Gly Ala Gly Met Asn Val Asp Pro Ala Thr Leu
                                105
Asp Ala Lys Ala Val Ala Val Tyr Ala Asp Gln Ala Lys Asp Gln Gly
                           120
Ile Val Ala Phe Ile Met Asp Val Ile Pro Ala Ser Val Ile Gly Ala
                       135
                                            140
Phe Ala Ser Gly Asn Ile Leu Gln Val Leu Leu Phe Ala Val Leu Phe
                   150
                                        155
Gly Phe Ala Leu His Arg Leu Gly Ser Lys Gly Gln Leu Ile Phe Asn
                165
                                    170
Val Ile Glu Ser Phe Ser Gln Val Ile Phe Gly Ile Ile Asn Met Ile
                                185
Met Arg Leu Ala Pro Ile Gly Ala Phe Gly Ala Met Ala Phe Thr Ile
                            200
Gly Lys Tyr Gly Val Gly Thr Leu Val Gln Leu Gly Gln Leu Ile Ile
                        215
Cys Phe Tyr Ile Thr Cys Ile Leu Phe Val Val Leu Val Leu Gly Ser
                   230
                                        235
Ile Ala Lys Ala Thr Gly Phe Ser Ile Phe Lys Phe Ile Arg Tyr Ile
               245
                                    250
Arg Glu Glu Leu Leu Ile Val Leu Gly Thr Ser Ser Ser Glu Ser Ala
           260
                               265
                                                    270
Leu Pro Arg Met Leu Asp Lys Met Glu Lys Leu Gly Cys Arg Lys Ser
                            280
Val Val Gly Leu Val Ile Pro Thr Gly Tyr Ser Phe Asn Leu Asp Gly
                        295
                                            300
Thr Ser Ile Tyr Leu Thr Met Ala Ala Val Phe Ile Ala Gln Ala Thr
                   310
                                        315
Asn Ser Gln Met Asp Ile Val His Gln Ile Thr Leu Leu Ile Val Leu
                325
                                   330
Leu Leu Ser Ser Lys Gly Ala Ala Gly Val Thr Gly Ser Gly Phe Ile
           340
                               345
                                                    350
Val Leu Ala Ala Thr Leu Ser Ala Val Gly His Leu Pro Val Ala Gly
                            360
Leu Ala Leu Ile Leu Gly Ile Asp Arg Phe Met Ser Glu Ala Arg Ala
                        375
                                            380
Leu Thr Asn Leu Val Gly Asn Gly Val Ala Thr Ile Val Val Ala Lys
                   390
                                       395
Trp Val Lys Glu Leu Asp His Lys Lys Leu Asp Asp Val Leu Asn Asn
               405
                                   410
Arg Ala Pro Asp Gly Lys Thr His Glu Leu Ser Ser
            420
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<210> 395

<211> 396

<212> PRT

<213> Escherichia coli

<400> 395

 Met Thr Thr Arg Gln His Ser Ser Phe Ala Ile Val Phe Ile Leu Gly

 1
 5
 10
 15

 Leu Leu Ala Met Leu Met Pro Leu Ser Ile Asp Met Tyr Leu Pro Ala 20
 25
 30

 Leu Pro Val Ile Ser Ala Gln Phe Gly Val Pro Ala Gly Ser Thr Gln 35
 40
 45

 Met Thr Leu Ser Thr Tyr Ile Leu Gly Phe Ala Leu Gly Gln Leu Ile 50
 55

```
Tyr Gly Pro Met Ala Asp Ser Phe Gly Arg Lys Pro Val Val Leu Gly
             70
Gly Thr Leu Val Phe Ala Ala Ala Ala Val Ala Cys Ala Leu Ala Asn
Thr Ile Asp Gln Leu Ile Val Met Arg Phe Phe His Gly Leu Ala Ala
                           105
         100
Ala Ala Ser Val Val Ile Asn Ala Leu Met Arg Asp Ile Tyr Pro
                        120
      115
Lys Glu Glu Phe Ser Arg Met Met Ser Phe Val Met Leu Val Thr Thr
                    135
                                      140
Ile Ala Pro Leu Met Ala Pro Ile Val Gly Gly Trp Val Leu Val Trp
                                 155
                150
Leu Ser Trp His Tyr Ile Phe Trp Ile Leu Ala Leu Ala Ala Ile Leu
         165
                               170
Ala Ser Ala Met Ile Phe Phe Leu Ile Lys Glu Thr Leu Pro Pro Glu
         180
                           185
Arg Arg Gln Pro Phe His Ile Arg Thr Thr Ile Gly Asn Phe Ala Ala
                        200
Leu Phe Arg His Lys Arg Val Leu Ser Tyr Met Leu Ala Ser Gly Phe
                    215
Ser Phe Ala Gly Met Phe Ser Phe Leu Ser Ala Gly Pro Phe Val Tyr
                230 235 240
Ile Glu Ile Asn His Val Ala Pro Glu Asn Phe Gly Tyr Tyr Phe Ala
             245 250
Leu Asn Ile Val Phe Leu Phe Val Met Thr Ile Phe Asn Ser Arg Phe
                           265
Val Arg Arg Ile Gly Ala Leu Asn Met Phe Arg Ser Gly Leu Trp Ile
                       280
Gln Phe Ile Met Ala Ala Trp Met Val Ile Ser Ala Leu Leu Gly Leu
                    295
                                     300
Gly Phe Trp Ser Leu Val Val Gly Val Ala Ala Phe Val Gly Cys Val
                 310
                                  315
Ser Met Val Ser Ser Asn Ala Met Ala Val Ile Leu Asp Glu Phe Pro
                              330
             325
His Met Ala Gly Thr Ala Ser Ser Leu Ala Gly Thr Phe Arg Phe Gly
       340
                           345
Ile Gly Ala Ile Val Gly Ala Leu Leu Ser Leu Ala Thr Phe Asn Ser
     355 360
Ala Trp Pro Met Ile Trp Ser Ile Ala Phe Cys Ala Thr Ser Ser Ile
 370 375 380
Leu Phe Cys Leu Tyr Ala Ser Arg Pro Lys Lys Arg
                 390
```

<210> 396

<211> 231

<212> PRT

<213> Escherichia coli

<400> 396

 Met
 Arg
 Leu
 Asp
 Lys
 Phe
 Ile
 Ala
 Gln
 Gln
 Leu
 Gly
 Val
 Ser
 Arg
 Ala

 Ile
 Ala
 Gly
 Asn
 Arg
 Val
 Thr
 Val
 Asp
 Gly
 Glu
 Glu
 Glu
 Glu
 Glu
 Glu
 Glu
 Glu
 Asp
 Glu
 Ala
 Ala

90 Ala Ala Gly Arg Leu Asp Ile Asp Thr Thr Gly Leu Val Leu Met Thr 105 Asp Asp Gly Gln Trp Ser His Arg Ile Thr Ser Pro Arg His His Cys 120 Glu Lys Thr Tyr Leu Val Thr Leu Glu Ser Pro Val Ala Asp Asp Thr 135 140 Ala Glu Gln Phe Ala Lys Gly Val Gln Leu His Asn Glu Lys Asp Leu 150 155 Thr Lys Pro Ala Val Leu Glu Val Ile Thr Pro Thr Gln Val Arg Leu 165 170 Thr Ile Ser Glu Gly Arg Tyr His Gln Val Lys Arg Met Phe Ala Ala 180 185 Val Gly Asn His Val Val Glu Leu His Arg Glu Arg Ile Gly Gly Ile 200 Thr Leu Asp Ala Asp Leu Ala Pro Gly Glu Tyr Arg Pro Leu Thr Glu 215 Glu Glu Ile Ala Ser Val Val 230

<210> 397

<211> 442

<212> PRT

<213> Escherichia coli

ZADON 397

Met Lys Lys Ile Glu Cys Ala Cys Asn Phe Leu Met Asp Lys Asp Ala Gln Gly Tyr Ile Asp Leu Ser Asp Leu Asp Leu Thr Ser Cys His Phe Lys Gly Asp Val Ile Ser Lys Val Ser Phe Leu Ser Ser Asn Leu Gln His Val Thr Phe Glu Cys Lys Glu Ile Gly Asp Cys Asn Phe Thr Thr 55 Ala Ile Val Asp Asn Val Ile Phe Arg Cys Arg Arg Leu His Asn Val 70 75 Ile Phe Ile Lys Ala Ser Gly Glu Cys Val Asp Phe Ser Lys Asn Ile 90 Leu Asp Thr Val Asp Phe Ser Gln Ser Gln Leu Gly His Ser Asn Phe 105 Arg Glu Cys Gln Ile Arg Asn Ser Asn Phe Asp Asn Cys Tyr Leu Tyr 120 125 Ala Ser His Phe Thr Arg Ala Glu Phe Leu Ser Ala Lys Glu Ile Ser 135 140 Phe Ile Lys Ser Asn Leu Thr Ala Val Met Phe Asp Tyr Val Arg Met 150 155 Ser Thr Gly Asn Phe Lys Asp Cys Ile Thr Glu Gln Leu Glu Leu Thr 170 165 Ile Asp Tyr Ser Asp Ile Phe Trp Asn Glu Asp Leu Asp Gly Tyr Ile 185 Asn Asn Ile Ile Lys Met Ile Asp Thr Leu Pro Asp Asn Ala Met Ile 200 Leu Lys Ser Val Leu Ala Val Lys Leu Val Met Gln Leu Lys Ile Leu 215 220 Asn Ile Val Asn Lys Asn Phe Ile Glu Asn Met Lys Lys Ile Phe Ser 235 230 His Cys Pro Tyr Ile Lys Asp Pro Ile Ile Arg Ser Tyr Ile His Ser 250 Asp Glu Asp Asn Lys Phe Asp Asp Phe Met Arg Gln His Arg Phe Ser 265

Glu Val Asn Phe Asp Thr Gln Gln Met Ile Asp Phe Ile Asn Arg Phe 280 Asn Thr Asn Lys Trp Leu Ile Asp Lys Asn Asn Asn Phe Phe Ile Gln 300 295 Leu Ile Asp Gln Ala Leu Arg Ser Thr Asp Asp Met Ile Lys Ala Asn 315 310 Val Trp His Leu Tyr Lys Glu Trp Ile Arg Ser Asp Asp Val Ser Pro 330 325 Ile Phe Ile Glu Thr Glu Asp Asn Leu Arg Thr Phe Asn Thr Asn Glu 345 350 Leu Thr Arg Asn Asp Asn Ile Phe Ile Leu Phe Ser Ser Val Asp Asp 360 Gly Pro Val Met Val Val Ser Ser Gln Arg Leu His Asp Met Leu Asn 380 375 Pro Thr Lys Asp Thr Asn Trp Asn Ser Thr Tyr Ile Tyr Lys Ser Arg 385 390 395 His Glu Met Leu Pro Val Asn Leu Thr Gln Glu Thr Leu Phe Ser Ser 410 405 Lys Ser His Gly Lys Tyr Ala Leu Phe Pro Ile Phe Thr Ala Ser Trp 425 420 Arg Ala His Arg Ile Met Asn Lys Gly Val 440

<210> 398 <211> 238 <212> PRT

<213> Escherichia coli

<400> 398

Met Gly Arg Lys Trp Ala Asn Ile Val Ala Lys Lys Thr Ala Lys Asp 10 Gly Ala Thr Ser Lys Ile Tyr Ala Lys Phe Gly Val Glu Ile Tyr Ala 25 Ala Ala Lys Gln Gly Glu Pro Asp Pro Glu Leu Asn Thr Ser Leu Lys 40 Phe Val Ile Glu Arg Ala Lys Gln Ala Gln Val Pro Lys His Val Ile 55 Asp Lys Ala Ile Asp Lys Ala Lys Gly Gly Gly Asp Glu Thr Phe Val 75 70 Gln Gly Arg Tyr Glu Gly Phe Gly Pro Asn Gly Ser Met Ile Ile Ala 85 Glu Thr Leu Thr Ser Asn Val Asn Arg Thr Ile Ala Asn Val Arg Thr 105 100 Ile Phe Asn Lys Lys Gly Gly Asn Ile Gly Ala Ala Gly Ser Val Ser 120 Tyr Met Phe Asp Asn Thr Gly Val Ile Val Phe Lys Gly Thr Asp Pro 130 135 Asp His Ile Phe Glu Ile Leu Leu Glu Ala Glu Val Asp Val Arg Asp 155 150 Val Thr Glu Glu Glu Gly Asn Ile Val Ile Tyr Thr Glu Pro Thr Asp 170 165 Leu His Lys Gly Ile Ala Ala Leu Lys Ala Ala Gly Ile Thr Glu Phe 180 185 Ser Thr Thr Glu Leu Glu Met Ile Ala Gln Ser Glu Val Glu Leu Ser 200 · 195 Pro Glu Asp Leu Glu Ile Phe Glu Gly Leu Val Asp Ala Leu Glu Asp 220 215 Asp Asp Asp Val Gln Lys Val Tyr His Asn Val Ala Asn Leu

<210> 399 <211> 261 <212> PRT <213> Escherichia coli <400> 399 Met Val Leu Met Ser Glu Thr Lys Asn Glu Leu Glu Asp Leu Leu Glu 10 Lys Ala Ala Thr Glu Pro Ala His Arg Pro Ala Phe Phe Arg Thr Leu 20 25 Leu Glu Ser Thr Val Trp Val Pro Gly Thr Ala Ala Gln Gly Glu Ala 40 Val Val Glu Asp Ser Ala Leu Asp Leu Gln His Trp Glu Lys Glu Asp 55 Gly Thr Ser Val Ile Pro Phe Phe Thr Ser Leu Glu Ala Leu Gln Gln 70 Ala Val Glu Asp Glu Gln Ala Phe Val Val Met Pro Val Arg Thr Leu 90 Phe Glu Met Thr Leu Gly Glu Thr Leu Phe Leu Asn Ala Lys Leu Pro 105 Thr Gly Lys Glu Phe Met Pro Arg Glu Ile Ser Leu Leu Ile Gly Glu 120 Glu Gly Asn Pro Leu Ser Ser Gln Glu Ile Leu Glu Gly Gly Glu Ser 135 140 Leu Ile Leu Ser Glu Val Ala Glu Pro Pro Ala Gln Met Ile Asp Ser 150 155 Leu Thr Thr Leu Phe Lys Thr Ile Lys Pro Val Lys Arg Ala Phe Ile 170 Cys Ser Ile Lys Glu Asn Glu Glu Ala Gln Pro Asn Leu Leu Ile Gly 185 Ile Glu Ala Asp Gly Asp Ile Glu Glu Ile Ile Gln Ala Thr Gly Ser 200 Val Ala Thr Asp Thr Leu Pro Gly Asp Glu Pro Ile Asp Ile Cys Gln 215 Val Lys Lys Gly Glu Lys Gly Ile Ser His Phe Ile Thr Glu His Ile 230 235 Ala Pro Phe Tyr Glu Arg Arg Trp Gly Gly Phe Leu Arg Asp Phe Lys 250 Gln Asn Arg Ile Ile 260 <210> 400 <211> 421 <212> PRT <213> Escherichia coli <400> 400 Met Leu Thr Lys Lys Lys Trp Ala Leu Phe Ser Leu Leu Thr Leu Cys 10 Gly Gly Thr Ile Tyr Lys Leu Pro Ser Leu Lys Asp Ala Phe Tyr Ile Pro Met Gln Glu Tyr Phe His Leu Thr Asn Gly Gln Ile Gly Asn Ala 40 Met Ser Val Asn Ser Phe Val Thr Thr Val Gly Phe Phe Leu Ser Ile 55 Tyr Phe Ala Asp Lys Leu Pro Arg Arg Tyr Thr Met Ser Phe Ser Leu 70 Ile Ala Thr Gly Leu Leu Gly Val Tyr Leu Thr Thr Met Pro Gly Tyr

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Trp Gly Ile Leu Phe Val Trp Ala Leu Phe Gly Val Thr Cys Asp Met
           100
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Met Asn Trp Pro Val Leu Leu Lys Ser Val Ser Arg Leu Gly Asn Ser
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Glu Gln Gln Gly Arg Leu Phe Gly Phe Phe Glu Thr Gly Arg Gly Ile
                      135
Val Asp Thr Val Val Ala Phe Ser Ala Leu Ala Val Phe Thr Trp Phe
                  150
                                      155
Gly Ser Gly Leu Leu Gly Phe Lys Ala Gly Ile Trp Phe Tyr Ser Leu
                                  170
Ile Val Ile Ala Val Gly Ile Ile Ile Phe Phe Val Leu Asn Asp Lys
                              185
Glu Glu Ala Pro Ser Val Glu Val Lys Lys Glu Asp Gly Ala Ser Lys
                       200
       195
Asn Thr Ser Met Thr Ser Val Leu Lys Asp Lys Thr Ile Trp Leu Ile
                       215
                                          220
Ala Phe Asn Val Phe Phe Val Tyr Ala Val Tyr Cys Gly Leu Thr Phe
                                      235
                  230
Phe Ile Pro Phe Leu Lys Asn Ile Tyr Leu Leu Pro Val Ala Leu Val
              245
                                  250
Gly Ala Tyr Gly Ile Ile Asn Gln Tyr Cys Leu Lys Met Ile Gly Gly
                             265 . 270
          260
Pro Ile Gly Gly Met Ile Ser Asp Lys Ile Leu Lys Ser Pro Ser Lys
                          280
Tyr Leu Cys Tyr Thr Phe Ile Ile Ser Thr Ala Ala Leu Val Leu Leu
                      295
Ile Met Leu Pro His Glu Ser Met Pro Val Tyr Leu Gly Met Ala Cys
                                      315
                  310
Thr Leu Gly Phe Gly Ala Ile Val Phe Thr Gln Arg Ala Val Phe Phe
              325
                                   330
Ala Pro Ile Gly Glu Ala Lys Ile Ala Glu Asn Lys Thr Gly Ala Ala
                              345
          340
Met Ala Leu Gly Ser Phe Ile Gly Tyr Ala Pro Ala Met Phe Cys Phe
                          360
Ser Leu Tyr Gly Tyr Ile Leu Asp Leu Asn Pro Gly Ile Ile Gly Tyr
                      375
Lys Ile Val Phe Gly Ile Met Ala Cys Phe Ala Phe Ser Gly Ala Val
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Val Ser Val Met Leu Val Lys Arg Ile Ser Gln Arg Lys Lys Glu Met
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Leu Ala Ala Glu Ala
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<212> PRT

<213> Escherichia coli

<400> 401

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 Leu
 Leu
 Thr
 Lys
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 Cys
 Trp
 Ile
 Thr
 Leu
 Ala
 Ala

 Ala
 Pro
 Phe
 Leu
 Phe
 Leu
 Ala
 Ala
 Trp
 Gly
 Ala
 Asp
 Lys
 Leu
 Trp

 Pro
 Leu
 Pro
 Leu
 His
 Glu
 Val
 Asn
 Pro
 Ala
 Arg
 Val
 Val
 Val
 Ala
 Glu
 Ala
 Glu
 Asp
 Ala
 Asp
 Ala
 Asp
 Ala
 Glu
 Ile
 Ile
 Ala
 Ile
 Ile

				85					90					95	
			Ala 100					105					110		
Ile	Ser	Gly 115	Gly	Ser	Thr	Leu	Thr 120	Met	Gln	Val	Ala	Arg 125	Leu	Leu	qeA
Pro	His 130	Pro	Lys	Thr	Phe	Gly 135	Gly	Lys	Ile	Arg	Gln 140	Leu	Trp	Arg	Ala
Leu 145	Gln	Leu	Glu	Trp	His 150	Leu	Ser	Lys	Arg	Glu 155	Ile	Leu	Thr	Leu	Tyr 160
Leu	Asn	Arg	Ala	Pro 165	Phe	Gly	Gly	Thr	Leu 170	Gln	Gly	Ile	Gly	Ala 175	Ala
Ser	Trp	Ala	Tyr 180	Leu	Gly	Lys	Ser	Pro 185	Ala	Asn	Leu	Ser	Tyr 190	Ser	Glu
Ala	Ala	Met 195	Leu	Ala	Val	Leu	Pro 200	Gln	Ala	Prọ	Ser	Arg 205	Leu	Arg	Pro
	210		Pro			215					220				
225			Val		230		_		_	235			_		240
			Pro	245					250					255	
			Ser 260					265					270		
		275	Leu				280					285			
	290	_	Lys	_		295					300				
305		_	His		310		_		_	315	_		_		320
			Asp	325				_	330		_			335	
			Pro 340					345					350		
	_	355	Gly				360					365			
	370		Gly			375					380				
385			Ser		390					395					400
			Val	405					410					415	
			Val 420					425					430		
		435					440					445			Met Leu
	450		-			455				_	460			_	Ser
465			Trp	-	470					475					480
_			Ser	485					490					495	
		_	500 Tyr				_	505					510	_	
		515	_	_			520		_			525			
	530					535					540				Val
545					550					555					Val 560
ASN	ASN	тте	Leu	565	ser	arg	ser	ATS	570	reg	PTO	стп	Asp	9ro 575	Arg

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Pro Asn Ser Val Thr Arg Gly Val Ile Cys Trp Pro Gly Gly Gln Ser
                             585
         580
Leu Pro Glu Gly Asp Gly Asn Cys Arg Arg Arg Leu Ala Thr Trp Leu
                          600
Leu Asp Gly Ser Gln Pro Pro Thr Leu Leu Leu Pro Glu Gln Glu Gly
                                        620
                     615
Ile Asn Gly Ile Arg Phe Pro Ile Trp Leu Asp Glu Asn Gly Lys Arg
                                    635
                  630
Val Ala Ala Asp Cys Pro Gln Ala Arg Gln Glu Met Ile Asn Val Trp
              645
                             650
Pro Leu Pro Leu Glu Pro Trp Leu Pro Ala Ser Glu Arg Arg Ala Val
                             665
          660
Arg Leu Pro Pro Ala Ser Thr Ser Cys Pro Pro Tyr Gly His Asp Ala
                         680
Gln Leu Pro Leu Gln Leu Thr Gly Val Arg Asp Gly Ala Ile Ile Lys
                     695
Arg Leu Pro Gly Ala Ala Glu Ala Thr Leu Pro Leu Gln Ser Ser Gly
                 710
Gly Ala Gly Glu Arg Trp Trp Phe Leu Asn Gly Glu Pro Leu Thr Glu
                                 730
              725
Arg Gly Arg Asn Val Thr Leu His Leu Thr Asp Lys Gly Asp Tyr Gln
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          740 745
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Met Gln
 770
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	210					215					220				
Ser 225	qaA	ГЛЗ	Leu	Leu	Gln 230	Met	Ala	Asp	Leu	Val 235	Tyr	Thr	Gly	Arg	Phe 240
Asp	Leu	Asn	Pro	Ala 245	Arg	Asn	Thr	Arg	Glu 250	Lys	Leu	Leu	Leu	Pro 255	Leu
Gly	Asp	Ile	Lуз 260	Pro	Leu	Gln	Gln	Ala 265	Gly	Val	Tyr	Leu	Ala 270	Val	Met
Asn	Gln	Ala 275	Gly	Arg	Tyr	Asp	Tyr 280	Ser	Asn	Pro	Ala	Thr 285	Leu	Phe	Thr
	290				Val	295					300				
Ile 305	Phe	Thr	Gln	Ser	Leu 310	Glu	Asn	Gly	Ala	Ala 315	Gln	Gln	Gly	Ile	Glu 320
				325	Glu				330					335	
_			340		Val			345			_		350		
		355			Asp		360					365			
	370				Ala	375					380			_	-
385					Met 390					395					400
				405	Asn	_			410	_				415	
			420		Ile			425			_		430	_	
Val	Leu	Arg 435	Ser	Val	Val	Ser	Gln 440	Pro	Glu	Asn	Gly	Leu 445	Tyr	His	Phe
	450			_	Ser	455					460				_
465					Asn 470					475					480
-				485	Arg				490					495	
			500		Asp			505					510		
		515			Ala		520					525			
	530			-	Glu	535					540	_			
545					Glu 550				_	555					560
				565	Lys				570					575	
_			580		Ser			585					590		
		595	_	_	Arg		600					605			
_	610		_		Leu	615			_		620				_
625				_	Arg 630					635					640
		_		645	Ala				650					655	
_		_	660		Val			665					670	_	
Arg	Arg	Asp 675	Tyr	Tyr	Trp	neA	Trp 680	Ser	Glu	Asp	Glu	Gly 685	Trp	Gln	Ser
Gln	Phe 690	Asp	Gln	Lys	Asp	Leu 695	Ile	Glu	Asn	Glu	Gln 700	Thr	Leu	Asp	Leu

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Tyr Arg Leu Glu Val Lys Ala Pro Asn Glu Ala Val Ser Ser Val Arg
           725
                         730
Phe Trp Ala Gly Tyr Ser Trp Gln Asp Asn Ser Asp Gly Ser Gly Ala
       740 745
Val Arg Pro Asp Arg Val Thr Leu Lys Leu Asp Lys Ala Ser Tyr Arg
          760
Pro Gly Asp Thr Ile Lys Leu His Ile Ala Ala Pro Thr Ala Gly Lys
      775
                               780
Gly Tyr Ala Met Val Glu Ser Ser Glu Gly Pro Leu Trp Trp Gln Glu
             790 795
Ile Asp Val Arg Ala Gln Gly Leu Asp Leu Thr Ile Pro Val Asp Lys
                         810
           805
Thr Trp Asn Arg His Asp Leu Tyr Leu Ser Thr Leu Val Val Arg Pro
            825
     820
Gly Asp Lys Ser Arg Ser Ala Thr Pro Lys Arg Ala Val Gly Val Leu
                   840
His Leu Pro Leu Gly Asp Glu Asn Arg Arg Leu Asp Leu Ala Leu Glu
                855
                     860
Thr Pro Ala Lys Met Arg Pro Asn Gln Pro Leu Thr Val Lys Ile Lys
   870 875 880
Ala Ser Thr Lys Asn Gly Glu Lys Pro Lys Gln Val Asn Val Leu Val
                     890
          885
Ser Ala Val Asp Ser Gly Val Leu Asn Ile Thr Asp Tyr Val Thr Pro
                      905
Asp Pro Trp Gln Ala Phe Phe Gly Gln Lys Arg Tyr Gly Ala Asp Ile
  915 920
Tyr Asp Ile Tyr Gly Gln Val Ile Glu Gly Gln Gly Arg Leu Ala Ala
 930 935
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Leu Arg Phe Gly Gly Asp Gly Asp Glu Leu Lys Arg Gly Gly Lys Pro
              950
                          955
Pro Val Asn His Val Asn Ile Val Val Gln Gln Ala Leu Pro Val Thr
                        970 .
   965
Leu Asn Glu Gln Gly Glu Gly Ser Val Thr Leu Pro Ile Gly Asp Phe
980 985
Asn Gly Glu Leu Arg Val Met Ala Gln Ala Trp Thr Ala Asp Asp Phe
     995 1000 1005
Gly Ser Asn Glu Ser Lys Val Ile Val Ala Ala Pro Val Ile Ala Glu
  1010 1015 1020
Leu Asn Met Pro Arg Phe Met Ala Ser Gly Asp Thr Ser Arg Leu Thr
1025 1030 1035 1040
Leu Asp Ile Thr Asn Leu Thr Asp Lys Pro Gln Lys Leu Asn Val Ala
     1045 1050 1055
Leu Thr Ala Ser Gly Leu Leu Glu Leu Val Ser Asp Ser Pro Ala Ala
 1060 1065 1070
Val Glu Leu Ala Pro Gly Val Arg Thr Thr Leu Phe Ile Pro Val Arg
 1075 1080 1085
Ala Leu Pro Gly Tyr Gly Asp Gly Glu Ile Gln Ala Thr Ile Ser Gly
 1090 1095 1100
Leu Ala Leu Pro Gly Glu Thr Val Ala Asp Gln His Lys Gln Trp Lys
              1110 1115
Ile Gly Val Arg Pro Ala Phe Pro Ala Gln Thr Val Asn Tyr Gly Thr
       1125 1130 1135
Ala Leu Gln Pro Gly Glu Thr Trp Ala Ile Pro Ala Asp Gly Leu Gln
   1140 1145 1150
Asn Phe Ser Pro Val Thr Leu Glu Gly Gln Leu Leu Leu Ser Gly Lys
 1155 1160
Pro Pro Leu Asn Ile Ala Arg Tyr Ile Lys Glu Leu Lys Ala Tyr Pro
 1170 1175 1180
Tyr Gly Cys Leu Glu Gln Thr Ala Ser Gly Leu Phe Pro Ser Leu Tyr
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1190 1195 Thr Asn Ala Ala Gln Leu Gln Ala Leu Gly Ile Lys Gly Asp Ser Asp 1205 1210 Glu Lys Arg Arg Ala Ser Val Asp Ile Gly Ile Ser Arg Leu Leu Gln 1220 1225 Met Gln Arg Asp Asn Gly Gly Phe Ala Leu Trp Asp Lys Asn Gly Asp 1235 1240 1245 Glu Glu Tyr Trp Leu Thr Ala Tyr Val Met Asp Phe Leu Val Arg Ala 1260 1250 1255 Gly Glu Gln Gly Tyr Ser Val Pro Thr Asp Ala Ile Asn Arg Gly Asn 1270 1275 Glu Arg Leu Leu Arg Tyr Leu Gln Asp Pro Gly Met Met Ser Ile Pro 1285 1290 Tyr Ala Asp Asn Leu Lys Ala Ser Lys Phe Ala Val Gln Ser Tyr Ala 1300 1305 1310 Ala Leu Val Leu Ala Arg Gln Gln Lys Ala Pro Leu Gly Ala Leu Arg 1320 1325 1315 Glu Ile Trp Glu His Arg Ala Asp Ala Ala Ser Gly Leu Pro Leu Leu 1330 1335 1340 Gln Leu Gly Val Ala Leu Lys Thr Met Gly Asp Ala Thr Arg Gly Glu 1350 1355 Glu Ala Ile Ala Leu Ala Leu Lys Thr Pro Arg Asn Ser Asp Glu Arg 1365 1370 Ile Trp Leu Gly Asp Tyr Gly Ser Ser Leu Arg Asp Asn Ala Leu Met 1380 1385 1390 Leu Ser Leu Leu Glu Glu Asn Lys Leu Leu Pro Asp Glu Gln Tyr Thr 1395 1400 1405 Leu Leu Asn Thr Leu Ser Gln Gln Ala Phe Gly Glu Arg Trp Leu Ser 1420 1410 1415 Thr Gln Glu Ser Asn Ala Leu Phe Leu Ala Ala Arg Thr Ile Gln Asp 1430 1435 1440 Leu Pro Gly Lys Trp Gln Ala Gln Thr Ser Phe Ser Ala Glu Gln Leu 1445 1450 1455 Thr Gly Glu Lys Ala Gln Asn Ser Asn Leu Asn Ser Asp Gln Leu Val 1460 1465 1470 Thr Leu Gln Val Ser Asn Ser Gly Asp Gln Pro Leu Trp Leu Arg Met 1475 1480 1485 Asp Ala Ser Gly Tyr Pro Gln Ser Ala Pro Leu Pro Ala Asn Asn Val 1490 1495 1500 Leu Gln Ile Glu Arg His Ile Leu Gly Thr Asp Gly Lys Ser Lys Ser 1505 1510 1515 1520 Leu Asp Ser Leu Arg Ser Gly Asp Leu Val Leu Val Trp Leu Gln Val 1525 1530 Lys Ala Ser Asn Ser Val Pro Asp Ala Leu Val Val Asp Leu Leu Pro 1540 1545 1550 Ala Gly Leu Glu Leu Glu Asn Gln Asn Leu Ala Asn Gly Ser Ala Ser 1555 1560 Leu Glu Gln Ser Gly Gly Glu Val Gln Asn Leu Leu Asn Gln Met Gln 1570 1575 1580 Gln Ala Ser Ile Lys His Ile Glu Phe Arg Asp Asp Arg Phe Val Ala 1585 1590 1595 Ala Val Ala Val Asp Glu Tyr Gln Pro Val Thr Leu Val Tyr Leu Ala 1605 1610 Arg Ala Val Thr Pro Gly Thr Tyr Gln Val Pro Gln Pro Met Val Glu 1620 1625 Ser Met Tyr Val Pro Gln Trp Arg Ala Thr Gly Ala Ala Glu Asp Leu 1635 1640 Leu Ile Val Arg Pro 1650

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105 Phe Ala Glu Ser Gly Glu Thr Cys Arg Ala Arg Glu Leu Glu Gln Cys 120 Leu Glu Asp Phe Tyr Asp Gln Gly Lys Glu Ser Val Arg Trp His Leu 135 140 Asp Leu His Thr Ala Ile Arg Gly Ser Leu His Pro Gln Phe Gly Val 150 155 Leu Pro Gln Arg Asp Ile Pro Trp Asp Glu Lys Phe Leu Thr Trp Leu 165 170 Gly Ala Ala Gly Leu Glu Ala Leu Val Phe His Gln Glu Pro Gly Gly 185 Thr Phe Thr His Phe Ser Ala Arg His Phe Gly Ala Leu Ala Cys Thr 195 200 Leu Glu Leu Gly Lys Ala Leu Pro Phe Gly Gln Asn Asp Leu Arg Gln 215 220 Phe Ala Val Thr Ala Ser Ala Ile Ala Ala Leu Leu Ser Gly Glu Ser 230 235 Val Gly Ile Val Arg Thr Pro Pro Leu Arg Tyr Arg Val Val Ser Gln 250 245 Ile Thr Arg His Ser Pro Ser Phe Glu Met His Met Ala Ser Asp Thr 265 260 Leu Asn Phe Met Pro Phe Glu Lys Gly Thr Leu Leu Ala Gln Asp Gly 280 Glu Glu Arg Phe Thr Val Thr His Asp Val Glu Tyr Val Leu Phe Pro 295 300 Asn Pro Leu Val Ala Leu Gly Leu Arg Ala Gly Leu Met Leu Glu Lys Ile Ser

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<211> 447

<212> PRT

<213> Escherichia coli

<400> 405

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Leu Phe Val Tyr Gly Arg Glu Glu Gly Asn Asp Thr Arg Pro Ser Arg
                        200
Tyr Pro Ala Arg Gln Thr Arg Glu Ala Ser Glu Ala Val Ala Arg Leu
                      215
Asn Gln Val Asn Pro Gln Gln Val Ile Phe Ala Gln Gln Asn Pro Asp
                                  235
                 230
Val Ile Asp Gln Gly Val Phe His Asn Asp Val Ile Ala Val Ser Asn
                                250
              245
Arg Gln Val Leu Phe Cys His Gln Gln Ala Phe Ala Arg Gln Ser Gln
                             265
Leu Leu Ala Asn Leu Arg Ala Arg Val Asn Gly Phe Met Ala Ile Glu
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Val Pro Ala Thr Gln Val Ser Val Ser Asp Thr Val Ser Thr Tyr Leu
                                         300
                      295
Phe Asn Ser Gln Leu Leu Ser Arg Asp Asp Gly Ser Met Met Leu Val
                                    315
                  310
Leu Pro Gln Glu Cys Arg Glu His Ala Gly Val Trp Gly Tyr Leu Asn
                                 330
               325
Glu Leu Leu Ala Ala Asp Asn Pro Ile Ser Glu Leu Lys Val Phe Asp
           340
                             345
Leu Arg Glu Ser Met Ala Asn Gly Gly Gly Pro Ala Cys Leu Arg Leu
       355 360 .
Arg Val Val Leu Thr Glu Glu Glu Arg Arg Ala Val Asn Pro Ala Val
                                         380
                   375
Met Met Asn Asp Thr Leu Phe Asn Ala Leu Asn Asp Trp Val Asp Arg
                                     395
               390
Tyr Tyr Arg Asp Arg Leu Thr Ala Ala Asp Leu Ala Asp Pro Gln Leu
                                 410
              405
Leu Arg Glu Gly Arg Glu Ala Leu Asp Val Leu Ser Gln Leu Leu Asn
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<211> 492

<212> PRT

<213> Escherichia coli

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165
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Gly Glu Ala Val Met Arg Leu Trp Gln Gln Ala Gly Leu Pro Pro Gly
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Val Leu Asn Leu Val Gln Gly Gly Arg Glu Thr Gly Gln Ala Leu Ser
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Ala Leu Glu Asp Leu Asp Gly Leu Leu Phe Thr Gly Ser Ala Asn Thr
                       215
Gly Tyr Gln Leu His Arg Gln Leu Ser Gly Gln Pro Glu Lys Ile Leu
                   230
                                       235
Ala Leu Glu Met Gly Gly Asn Asn Pro Leu Ile Ile Asp Glu Val Ala
                                   250
Asp Ile Asp Ala Ala Val His Leu Thr Ile Gln Ser Ala Phe Val Thr
                               265
Ala Gly Gln Arg Cys Thr Cys Ala Arg Arg Leu Leu Lys Ser Gly
                           280
Ala Gln Gly Asp Ala Phe Leu Ala Arg Leu Val Ala Val Ser Gln Arg
                       295
                                           300
Leu Thr Pro Gly Asn Trp Asp Asp Glu Pro Gln Pro Phe Ile Gly Gly
                   310
                                       315
Leu Ile Ser Glu Gln Ala Ala Gln Gln Val Val Thr Ala Trp Gln Gln
               325
                                   330
Leu Glu Ala Met Gly Gly Arg Pro Leu Leu Ala Pro Arg Leu Leu Gln
           340
                               345
Ala Gly Thr Ser Leu Leu Thr Pro Gly Ile Ile Glu Met Thr Gly Val
                           360
Ala Gly Val Pro Asp Glu Glu Val Phe Gly Pro Leu Leu Arg Val Trp
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                                           380
Arg Tyr Asp Thr Phe Asp Glu Ala Ile Arg Met Ala Asn Asn Thr Arg
                   390
                                       395
Phe Gly Leu Ser Cys Gly Leu Val Ser Pro Glu Arg Glu Lys Phe Asp
               405
                                   410
Gln Leu Leu Glu Ala Arg Ala Gly Ile Val Asn Trp Asn Lys Pro
                              425
           420
Leu Thr Gly Ala Ala Ser Thr Ala Pro Phe Gly Gly Ile Gly Ala Ser
                           440
Gly Asn His Arg Pro Ser Ala Trp Tyr Ala Ala Asp Tyr Cys Ala Trp
                       455
Pro Met Ala Ser Leu Glu Ser Asp Ser Leu Thr Leu Pro Ala Thr Leu
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Asn Pro Gly Leu Asp Phe Ser Asp Glu Val Val Arg
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<212> PRT

<213> Escherichia coli

<400> 407

 Met
 Wet
 Val
 Ile
 Arg
 Pro
 Val
 Glu
 Arg
 Ser
 Asp
 Val
 Ser
 Ala
 Leu
 Met

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Ala Ser Lys Glu Leu Asn Val Tyr Asn Ala Leu Pro Thr Leu Phe Leu 100 105 Ser Asn Asp His Thr Gly Ser Ser Glu Leu Cys Thr Leu Phe Leu Asp 120 Pro Asp Trp Arg Lys Glu Gly Asn Gly Tyr Leu Leu Ser Lys Ser Arg 135 Phe Met Phe Met Ala Ala Phe Arg Asp Lys Phe Asn Asp Lys Val Val 150 155 Ala Glu Met Arg Gly Val Ile Asp Glu His Gly Tyr Ser Pro Phe Trp 165 170 Gln Ser Leu Gly Lys Arg Phe Phe Ser Met Asp Phe Ser Arg Ala Asp 185 Phe Leu Cys Gly Thr Gly Gln Lys Ala Phe Ile Ala Glu Leu Met Pro 205 200 Lys His Pro Ile Tyr Thr His Phe Leu Ser Gln Glu Ala Gln Asp Val 215 220 Ile Gly Gln Val His Pro Gln Thr Ala Pro Ala Arg Ala Val Leu Glu 230 235 Lys Glu Gly Phe Arg Tyr Arg Asn Tyr Ile Asp Ile Phe Asp Gly Gly 250 Pro Thr Leu Glu Cys Asp Ile Asp Arg Val Arg Ala Ile Arg Lys Ser 265 260 Arg Leu Val Glu Val Ala Glu Gly Gln Pro Ala Gln Gly Asp Phe Pro 280 285 275 Ala Cys Leu Val Ala Asn Glu Asn Tyr His His Phe Arg Val Val Leu 300 295 Val Arg Thr Asp Pro Ala Thr Glu Arg Leu Ile Leu Thr Ala Ala Gln 315 310 Leu Asp Ala Leu Lys Cys His Ala Gly Asp Arg Val Arg Leu Val Arg 325 330 Leu Cys Ala Glu Glu Lys Thr Ala 340

<210> 408

<211> 406

<212> PRT

<213> Escherichia coli

<400> 408

Met Ser Gln Pro Ile Thr Arg Glu Asn Phe Asp Glu Trp Met Ile Pro 10 Val Tyr Ala Pro Ala Pro Phe Ile Pro Val Arg Gly Glu Gly Ser Arg Leu Trp Asp Gln Gln Gly Lys Glu Tyr Ile Asp Phe Ala Gly Gly Ile 40 Ala Val Asn Ala Leu Gly His Ala His Pro Glu Leu Arg Glu Ala Leu 55 Asn Glu Gln Ala Ser Lys Phe Trp His Thr Gly Asn Gly Tyr Thr Asn Glu Pro Val Leu Arg Leu Ala Lys Lys Leu Ile Asp Ala Thr Phe Ala 90 Asp Arg Val Phe Phe Cys Asn Ser Gly Ala Glu Ala Asn Glu Ala Ala 105 Leu Lys Leu Ala Arg Lys Phe Ala His Asp Arg Tyr Gly Ser His Lys 120 ' Ser Gly Ile Val Ala Phe Lys Asn Ala Phe His Gly Arg Thr Leu Phe 135 140 Thr Val Ser Ala Gly Gly Gln Pro Ala Tyr Ser Gln Asp Phe Ala Pro 155 150 Leu Pro Ala Asp Ile Arg His Ala Ala Tyr Asn Asp Ile Asn Ser Ala

170 Ser Ala Leu Ile Asp Asp Ser Thr Cys Ala Val Ile Val Glu Pro Ile 185 Gin Gly Gly Gly Val Val Pro Ala Ser Asn Ala Phe Leu Gin Gly 200 Leu Arg Glu Leu Cys Asn Arg His Asn Ala Leu Leu Ile Phe Asp Glu 215 220 Val Gln Thr Gly Val Gly Arg Thr Gly Glu Leu Tyr Ala Tyr Met His 230 235 Tyr Gly Val Thr Pro Asp Leu Leu Thr Thr Ala Lys Ala Leu Gly Gly 245 250 Gly Phe Pro Val Gly Ala Leu Leu Ala Thr Glu Glu Cys Ala Arg Val 265 Met Thr Val Gly Thr His Gly Thr Thr Tyr Gly Gly Asn Pro Leu Ala 280 Ser Ala Val Ala Gly Lys Val Leu Glu Leu Ile Asn Thr Pro Glu Met 295 Leu Asn Gly Val Lys Gln Arg His Asp Trp Phe Val Glu Arg Leu Asn 310 315 Thr Ile Asn His Arg Tyr Gly Leu Phe Ser Glu Val Arg Gly Leu Gly 325 330 Leu Leu Ile Gly Cys Val Leu Asn Ala Asp Tyr Ala Gly Gln Ala Lys 340 345 Gln Ile Ser Gln Glu Ala Ala Lys Ala Gly Val Met Val Leu Ile Ala 360 Gly Gly Asn Val Val Arg Phe Ala Pro Ala Leu Asn Val Ser Glu Glu 375 380 Glu Val Thr Thr Gly Leu Asp Arg Phe Ala Ala Ala Cys Glu His Phe 390 395 Val Ser Arg Gly Ser Ser 405

<210> 409 <211> 1048 <212> PRT

<213> Escherichia coli

<400> 409

Met Lys Ile Leu Ser Leu Arg Leu Lys Asn Leu Asn Ser Leu Lys Gly Glu Trp Lys Ile Asp Phe Thr Arg Glu Pro Phe Ala Ser Asn Gly Leu Phe Ala Ile Thr Gly Pro Thr Gly Ala Gly Lys Thr Thr Leu Leu Asp Ala Ile Cys Leu Ala Leu Tyr His Glu Thr Pro Arg Leu Ser Asn Val 55 Ser Gln Ser Gln Asn Asp Leu Met Thr Arg Asp Thr Ala Glu Cys Leu Ala Glu Val Glu Phe Glu Val Lys Gly Glu Ala Tyr Arg Ala Phe Trp Ser Gln Asn Arg Ala Arg Asn Gln Pro Asp Gly Asn Leu Gln Val Pro 105 Arg Val Glu Leu Ala Arg Cys Ala Asp Gly Lys Ile Leu Ala Asp Lys 120 Val Lys Asp Lys Leu Glu Leu Thr Ala Thr Leu Thr Gly Leu Asp Tyr 135 140 Gly Arg Phe Thr Arg Ser Met Leu Leu Ser Gln Gly Gln Phe Ala Ala 150 155 Phe Leu Asn Ala Lys Pro Lys Glu Arg Ala Glu Leu Leu Glu Glu Leu 170

WO 01/48209 PCT/US00/34419.

	Thr	Gly	Thr	Glu 180	Ile	Тут	Gly	Gln	Ile 185	Ser	Ala	Met	Val	Phe 190	Glu	Gln
	His	Lys	Ser 195	Ala	Arg	Thr	Glu	Leu 200	Glu	Lys	Leu	Gln	Ala 205	G1n	Ala	Ser
•	Gly	Val 210		Leu	Leu	Thr	Pro 215		Gln	Val	Gln	Ser 220		Thr	Ala	Ser
	Leu 225		Val	Leu	Thr	Asp 230	Glu	Glu	Lys	Gln	Leu 235	Ile	Thr	Ala	Gln	Gln 240
		Glu	Gln	Gln	Ser 245	Leu	Asn	Trp	Leu	Thr 250	Arg	Gln	Asp	Glu	Leu 255	Gln
	Gln	Glu	Ala	Ser 260	Arg	Arg	Gln	Gln	Ala 265	Leu	Gln	Gln	Ala	Leu 270	Ala	Glu
			275					280					285		Gln	
		290					295					300			Ser	
	305					310					315				Arg	320
					325					330					Ala 335	
				340		4			345					350	Trp	•
			355	_				360			•		365		Gly	
	_	370					375					380			Arg	
	385					390					395				Leu	400
					405					410					Leu 415	
				420					425					430	Leu	
	-		435					440					445		Val	
		450					455					460			Leu	
	465					470					475				Asp Ala	480
	-			_	485					490					495 Ser	٠.,
	_			500			-		505	•				510		Asn
			515					520					525			Glu
		530	_				535					540				Leu
	545	_				550					555					560 Ala
					565					570					575	Leu
				580	-				585					590		His
			595			•		600					605			Gln
		610					615	•				620				Glu
	625					630					635					640 Thr
					645		•	•		650					655	
					-					_						

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665
Glu Ala Gln Ser Trp Gln Gln Arg Gln Asn Glu Leu Thr Ala Leu Gln
                           680
Asn Arg Ile Gln Gln Leu Thr Pro Ile Leu Glu Thr Leu Pro Gln Ser
                       695
Asp Glu Leu Pro His Cys Glu Glu Thr Val Val Leu Glu Asn Trp Arg
                   710
                                      715
Gln Val His Glu Gln Cys Leu Ala Leu His Ser Gln Gln Gln Thr Leu
                                  730
Gln Gln Gln Asp Val Leu Ala Ala Gln Ser Leu Gln Lys Ala Gln Ala
                               745
Gln Phe Asp Thr Ala Leu Gln Ala Ser Val Phe Asp Asp Gln Gln Ala
                           760
Phe Leu Ala Ala Leu Met Asp Glu Gln Thr Leu Thr Gln Leu Glu Gln
                       775
Leu Lys Gln Asn Leu Glu Asn Gln Arg Arg Gln Ala Gln Thr Leu Val
                   790
                                       795
Thr Gln Thr Ala Glu Thr Leu Ala Gln His Gln Gln His Arg Pro Asp
               805
                                  810
Asp Gly Leu Ala Leu Thr Val Thr Val Glu Gln Ile Gln Glu Leu
                              825
Ala Gln Thr His Gln Lys Leu Arg Glu Asn Thr Thr Ser Gln Gly Glu
                          840
Ile Arg Gln Gln Leu Lys Gln Asp Ala Asp Asn Arg Gln Gln Gln Gln
                      855
                                          860
Thr Leu Met Gln Gln Ile Ala Gln Met Thr Gln Gln Val Glu Asp Trp
                  870
                                      875
Gly Tyr Leu Asn Ser Leu Ile Gly Ser Lys Glu Gly Asp Lys Phe Arg
              885
                                  890
Lys Phe Ala Gln Gly Leu Thr Leu Asp Asn Leu Val His Leu Ala Asn
                              905
Gln Gln Leu Thr Arg Leu His Gly Arg Tyr Leu Leu Gln Arg Lys Ala
                           920
                                              925
Ser Glu Ala Leu Glu Val Glu Val Val Asp Thr Trp Gln Ala Asp Ala
                      935
                                           940
Val Arg Asp Thr Arg Thr Leu Ser Gly Gly Glu Ser Phe Leu Val Ser
                  950
                                      955
Leu Ala Leu Ala Leu Ser Asp Leu Val Ser His Lys Thr Arg
                                  970
               965
Ile Asp Ser Leu Phe Leu Asp Glu Gly Phe Gly Thr Leu Asp Ser Glu
                              985
Thr Leu Asp Thr Ala Leu Asp Ala Leu Asp Ala Leu Asn Ala Ser Gly
                          1000
Lys Thr Ile Gly Val Ile Ser His Val Glu Ala Met Lys Glu Arg Ile
                      1015
                                          1020
Pro Val Gln Ile Lys Val Lys Lys Ile Asn Gly Leu Gly Tyr Ser Lys
                                      1035
                  1030
Leu Glu Ser Thr Phe Ala Val Lys
               1045
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<210> 410

<211> 400

<212> PRT

<213> Escherichia coli

<400> 410

Met Arg Ile Leu His Thr Ser Asp Trp His Leu Gly Gln Asn Phe Tyr 1 5 10 15

Ser Lys Ser Arg Glu Ala Glu His Gln Ala Phe Leu Asp Trp Leu Leu 20 25 30

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Glu Thr Ala Gln Thr His Gln Val Asp Ala Ile Ile Val Ala Gly Asp
                         40
Val Phe Asp Thr Gly Ser Pro Pro Ser Tyr Ala Arg Thr Leu Tyr Asn
Arg Phe Val Val Asn Leu Gln Gln Thr Gly Cys His Leu Val Val Leu
               70
Ala Gly Asn His Asp Ser Val Ala Thr Leu Asn Glu Ser Arg Asp Ile
                                 90
Met Ala Phe Leu Asn Thr Thr Val Val Ala Ser Ala Gly His Ala Pro
          100
                              105
Gln Ile Leu Pro Arg Arg Asp Gly Thr Pro Gly Ala Val Leu Cys Pro
                          120
       115
Ile Pro Phe Leu Arg Pro Arg Asp Ile Ile Thr Ser Gln Ala Gly Leu
                                         140
                      135
Asn Gly Ile Glu Lys Gln Gln His Leu Leu Ala Ala Ile Thr Asp Tyr
                                     155
                  150
Tyr Gln Gln His Tyr Ala Asp Ala Cys Lys Leu Arg Gly Asp Gln Pro
                                 170
               165
Leu Pro Ile Ile Ala Thr Gly His Leu Thr Thr Val Gly Ala Ser Lys
                          185
          180
Ser Asp Ala Val Arg Asp Ile Tyr Ile Gly Thr Leu Asp Ala Phe Pro
                      . 200
       195
Ala Gln Asn Phe Pro Pro Ala Asp Tyr Ile Ala Leu Gly His Ile His
                      215
Arg Ala Gln Ile Ile Gly Gly Met Glu His Val Arg Tyr Cys Gly Ser
                                     235
                  230
Pro Ile Pro Leu Ser Phe Asp Glu Cys Gly Lys Ser Lys Tyr Val His
                                 250
             245
Leu Val Thr Phe Ser Asn Gly Lys Leu Glu Ser Val Glu Asn Leu Asn
                              265
          260
Val Pro Val Thr Gln Pro Met Ala Val Leu Lys Gly Asp Leu Ala Ser
                          280
Ile Thr Ala Gln Leu Glu Gln Trp Arg Asp Val Ser Gln Glu Pro Pro
                      295
Val Trp Leu Asp Ile Glu Ile Thr Thr Asp Glu Tyr Leu His Asp Ile
                                      315
                  310
Gln Arg Lys Ile Gln Ala Leu Thr Glu Ser Leu Pro Val Glu Val Leu
              325 .
                                  330
Leu Val Arg Arg Ser Arg Glu Gln Arg Glu Arg Val Leu Ala Ser Gln
                             345
          340
Gln Arg Glu Thr Leu Ser Glu Leu Ser Val Glu Glu Val Phe Asn Arg
                         360
Arg Leu Ala Leu Glu Glu Leu Asp Glu Ser Gln Gln Gln Arg Leu Gln
  370 375
His Leu Phe Thr Thr Leu His Thr Leu Ala Gly Glu His Glu Ala
                  390
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<210> 411

<211> 254

<212> PRT

<213> Escherichia coli

<400> 411

Phe Asn Val Thr His Lys His Glu Ile Asp Ala Ala Val Glu His Ile Glu Lys Asp Ile Gly Pro Ile Asp Val Leu Val Asn Asn Ala Gly Ile Gln Arg Arg His Pro Phe Thr Glu Phe Pro Glu Gln Glu Trp Asn Asp 105 Val Ile Ala Val Asn Gln Thr Ala Val Phe Leu Val Ser Gln Ala Val 120 Thr Arg His Met Val Glu Arg Lys Ala Gly Lys Val Ile Asn Ile Cys 135 140 Ser Met Gln Ser Glu Leu Gly Arg Asp Thr Ile Thr Pro Tyr Ala Ala 150 155 Ser Lys Gly Ala Val Lys Met Leu Thr Arg Gly Met Cys Val Glu Leu 170 165 Ala Arg His Asn Ile Gln Val Asn Gly Ile Ala Pro Gly Tyr Phe Lys 185 Thr Glu Met Thr Lys Ala Leu Val Glu Asp Glu Ala Phe Thr Ala Trp 200 Leu Cys Lys Arg Thr Pro Ala Ala Arg Trp Gly Asp Pro Gln Glu Leu 215 220 Ile Gly Ala Ala Val Phe Leu Ser Ser Lys Ala Ser Asp Phe Val Asn 230 235 Gly His Leu Leu Phe Val Asp Gly Gly Met Leu Val Ala Val 245

<210> 412

<211> 343

<212> PRT

<213> Escherichia coli

<400> 412

Met Gln Val Lys Thr Gln Ser Cys Val Val Ala Gly Lys Lys Thr Val 10 Ala Val Thr Glu Gln Thr Ile Asp Trp Asn Asn Asn Gly Thr Leu Val Gln Ile Thr Arg Gly Gly Ile Cys Gly Ser Asp Leu His Tyr Tyr Gln Glu Gly Lys Val Gly Asn Phe Met Ile Lys Ala Pro Met Val Leu Gly 55 His Glu Val Ile Gly Lys Val Ile His Ser Asp Ser Ser Glu Leu His Glu Gly Gln Thr Val Ala Ile Asn Pro Ser Lys Pro Cys Gly His Cys 90 Lys Tyr Cys Ile Glu His Asn Glu Asn Gln Cys Thr Asp Met Arg Phe 105 Phe Gly Ser Ala Met Tyr Phe Pro His Val Asp Gly Gly Phe Thr Arg 120 Tyr Lys Met Val Glu Thr Ser Gln Cys Val Pro Tyr Pro Ala Lys Ala 135 Asp Glu Lys Val Met Ala Phe Ala Glu Pro Leu Ala Val Ala Ile His 155 Ala Ala His Gln Ala Gly Glu Leu Gln Gly Lys Arg Val Phe Ile Ser 170 Gly Val Gly Pro Ile Gly Cys Leu Ile Val Ser Ala Val Lys Thr Leu 185 Gly Ala Ala Glu Ile Val Cys Ala Asp Val Ser Pro Arg Ser Leu Ser 200 Leu Gly Lys Glu Met Gly Ala Asp Val Leu Val Asn Pro Gln Asn Asp 210

Asp Met Asp His Trp Lys Ala Glu Lys Gly Tyr Phe Asp Val Ser Phe 235 230 Glu Val Ser Gly His Pro Ser Ser Val Asn Thr Cys Leu Glu Val Thr 245 250 Arg Ala Arg Gly Val Met Val Gln Val Gly Met Gly Gly Ala Met Ala 265 260 Glu Phe Pro Met Met Thr Leu Ile Gly Lys Glu Ile Ser Leu Arg Gly 280 285 Ser Phe Arg Phe Thr Ser Glu Phe Asn Thr Ala Val Ser Trp Leu Ala 300 295 Asn Gly Val Ile Asn Pro Leu Pro Leu Ser Ala Glu Tyr Pro Phe 310 315 Thr Asp Leu Glu Glu Ala Leu Arg Phe Ala Gly Asp Lys Thr Gln Ala 330 325 Ala Lys Val Gln Leu Val Phe 340

<210> 413 <211> 548

<212> PRT

<213> Escherichia coli

<400> 413

Met Asp Ser Gln Arg Asn Leu Leu Val Ile Ala Leu Leu Phe Val Ser 10 Phe Met Ile Trp Gln Ala Trp Glu Gln Asp Lys Asn Pro Gln Pro Gln 25 Ala Gln Gln Thr Thr Gln Thr Thr Thr Ala Ala Gly Ser Ala Ala 40 Asp Gln Gly Val Pro Ala Ser Gly Gln Gly Lys Leu Ile Ser Val Lys 55 Thr Asp Val Leu Asp Leu Thr Ile Asn Thr Arg Gly Gly Asp Val Glu 70 Gln Ala Leu Leu Pro Ala Tyr Pro Lys Glu Leu Asn Ser Thr Gln Pro 90 Phe Gln Leu Leu Glu Thr Ser Pro Gln Phe Ile Tyr Gln Ala Gln Ser 105 100 Gly Leu Thr Gly Arg Asp Gly Pro Asp Asn Pro Ala Asn Gly Pro Arg 120 115 Pro Leu Tyr Asn Val Glu Lys Asp Ala Tyr Val Leu Ala Glu Gly Gln . . -135 140 Asn Glu Leu Gln Val Pro Met Thr Tyr Thr Asp Ala Ala Gly Asn Thr 150 155 Phe Thr Lys Thr Phe Val Leu Lys Arg Gly Asp Tyr Ala Val Asn Val 170 165 Asn Tyr Asn Val Glm Asn Ala Gly Glu Lys Pro Leu Glu Ile Ser Ser 185 Phe Gly Gln Leu Lys Gln Ser Ile Thr Leu Pro Pro His Leu Asp Thr · 200 Gly Ser Ser Asn Phe Ala Leu His Thr Phe Arg Gly Ala Ala Tyr Ser 215 Thr Pro Asp Glu Lys Tyr Glu Lys Tyr Lys Phe Asp Thr Ile Ala Asp 230 235 240 Asn Glu Asn Leu Asn Ile Ser Ser Lys Gly Gly Trp Val Ala Met Leu 245 250 Gln Gln Tyr Phe Ala Thr Ala Trp Ile Pro His Asn Asp Gly Thr Asn 265 Asn Phe Tyr Thr Ala Asn Leu Gly Asn Gly Ile Ala Ala Ile Gly Tyr 280 Lys Ser Gln Pro Val Leu Val Gln Pro Gly Gln Thr Gly Ala Met Asn

295 300 Ser Thr Leu Trp Val Gly Pro Glu Ile Gln Asp Lys Met Ala Ala Val 310 315 Ala Pro His Leu Asp Leu Thr Val Asp Tyr Gly Trp Leu Trp Phe Ile 330 Ser Gln Pro Leu Phe Lys Leu Leu Lys Trp Ile His Ser Phe Val Gly 345 Asn Trp Gly Phe Ser Ile Ile Ile Ile Thr Phe Ile Val Arg Gly Ile 360 Met Tyr Pro Leu Thr Lys Ala Gln Tyr Thr Ser Met Ala Lys Met Arg 375 Met Leu Gln Pro Lys Ile Gln Ala Met Arg Glu Arg Leu Gly Asp Asp 390 395 Lys Gln Arg Ile Ser Gln Glu Met Met Ala Leu Tyr Lys Ala Glu Lys 405 410 Val Asn Pro Leu Gly Gly Cys Phe Pro Leu Leu Ile Gln Met Pro Ile 425 Phe Leu Ala Leu Tyr Tyr Met Leu Met Gly Ser Val Glu Leu Arg Gln 440 Ala Pro Phe Ala Leu Trp Ile His Asp Leu Ser Ala Gln Asp Pro Tyr 455 460 Tyr Ile Leu Pro Ile Leu Met Gly Val Thr Met Phe Phe Ile Gln Lys 470 475 Met Ser Pro Thr Thr Val Thr Asp Pro Met Gln Gln Lys Ile Met Thr 485 490 Phe Met Pro Val Ile Phe Thr Val Phe Phe Leu Trp Phe Pro Ser Gly 505 500 510 Leu Val Leu Tyr Tyr Ile Val Ser Asn Leu Val Thr Ile Ile Gln Gln 520 525 Gln Leu Ile Tyr Arg Gly Leu Glu Lys Arg Gly Leu His Ser Arg Glu 530 535 Lys Lys Lys Ser 545

<210> 414

<211> 542

<212> PRT

<213> Escherichia coli

## <400> 414

Met Lys Thr Arg Asp Ser Gln Ser Ser Asp Val Ile Ile Ile Gly Gly Gly Ala Thr Gly Ala Gly Ile Ala Arg Asp Cys Ala Leu Arg Gly Leu Arg Val Ile Leu Val Glu Arg His Asp Ile Ala Thr Gly Ala Thr Gly 40 Arg Asn His Gly Leu Leu His Ser Gly Ala Arg Tyr Ala Val Thr Asp 55 Ala Glu Ser Ala Arg Glu Cys Ile Ser Glu Asn Gln Ile Leu Lys Arg Ile Ala Arg His Cys Val Glu Pro Thr Asn Gly Leu Phe Ile Thr Leu Pro Glu Asp Asp Leu Ser Phe Gln Ala Thr Phe Ile Arg Ala Cys Glu 105 Glu Ala Gly Ile Ser Ala Glu Ala Ile Asp Pro Gln Gln Ala Arg Ile 120 Ile Glu Pro Ala Val Asn Pro Ala Leu Ile Gly Ala Val Lys Val Pro 135 Asp Gly Thr Val Asp Pro Phe Arg Leu Thr Ala Ala Asn Met Leu Asp 155 150

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Ala Lys Glu His Gly Ala Val Ile Leu Thr Ala His Glu Val Thr Gly
                165
                                    170
Leu Ile Arq Glu Gly Ala Thr Val Cys Gly Val Arg Val Arg Asn His
                                185
Leu Thr Gly Glu Thr Gln Ala Leu His Ala Pro Val Val Val Asn Ala
       195
                            200
Ala Gly Ile Trp Gly Gln His Ile Ala Glu Tyr Ala Asp Leu Arg Ile
                        215
Arg Met Phe Pro Ala Lys Gly Ser Leu Leu Ile Met Asp His Arg Ile
                    230
                                        235
Asn Gln His Val Ile Asn Arg Cys Arg Lys Pro Ser Asp Ala Asp Ile
                                    250
Leu Val Pro Gly Asp Thr Ile Ser Leu Ile Gly Thr Thr Ser Leu Arg
                            . 265
Ile Asp Tyr Asn Glu Ile Asp Asp Asn Arg Val Thr Ala Glu Glu Val
       275
                            280
Asp Ile Leu Leu Arg Glu Gly Glu Lys Leu Ala Pro Val Met Ala Lys
                        295
Thr Arg Ile Leu Arg Ala Tyr Ser Gly Val Arg Pro Leu Val Ala Ser
                    310
                                        315
Asp Asp Asp Pro Ser Gly Arg Asn Val Ser Arg Gly Ile Val Leu Leu
                                    330
Asp His Ala Glu Arg Asp Gly Leu Asp Gly Phe Ile Thr Ile Thr Gly
                                345
Gly Lys Leu Met Thr Tyr Arg Leu Met Ala Glu Trp Ala Thr Asp Ala
Val Cys Arg Lys Leu Gly Asn Thr Arg Pro Cys Thr Thr Ala Asp Leu
                        375
Ala Leu Pro Gly Ser Gln Glu Pro Ala Glu Val Thr Leu Arg Lys Val
Ile Ser Leu Pro Ala Pro Leu Arg Gly Ser Ala Val Tyr Arg His Gly
                                    410
Asp Arg Thr Pro Ala Trp Leu Ser Glu Gly Arg Leu His Arg Ser Leu
            420
                                425
Val Cys Glu Cys Glu Ala Val Thr Ala Gly Glu Val Gln Tyr Ala Val
                            440
Glu Asn Leu Asn Val Asn Ser Leu Leu Asp Leu Arg Arg Arg Thr Arg
Val Gly Met Gly Thr Cys Gln Gly Glu Leu Cys Ala Cys Arg Ala Ala
                    470
                                        475
Gly Leu Leu Gln Arg Phe Asn Val Thr Thr Ser Ala Gln Ser Ile Glu
                485
                                    490
Gln Leu Ser Thr Phe Leu Asn Glu Arg Trp Lys Gly Val Gln Pro Ile
                                505
Ala Trp Gly Asp Ala Leu Arg Glu Ser Glu Phe Thr Arg Trp Val Tyr
Gln Gly Leu Cys Gly Leu Glu Lys Glu Gln Lys Asp Ala Leu
                        535
                                            540
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<210> 415

<211> 419

<212> PRT

<213> Escherichia coli

<400> 415

 Met Arg Phe Asp Thr Val Ile Met Gly Gly Gly Leu Ala Gly Leu Leu

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 Cys Gly Leu Gln Leu Gln Lys His Gly Leu Arg Cys Ala Ile Val Thr

 20
 25

 Arg Gly Gln Ser Ala Leu His Phe Ser Ser Gly Ser Leu Asp Leu Leu

```
40
Ser His Leu Pro Asp Gly Gln Pro Val Thr Asp Ile His Ser Gly Leu
Glu Ser Leu Arg Gln Gln Ala Pro Ala His Pro Tyr Ser Leu Leu Glu
                   70
Pro Gln Arg Val Leu Asp Leu Ala Cys Gln Ala Gln Ala Leu Ile Ala
                                   90
Glu Ser Gly Ala Gln Leu Gln Gly Ser Val Glu Leu Ala His Gln Arg
                               105
Val Thr Pro Leu Gly Thr Leu Arg Ser Thr Trp Leu Ser Ser Pro Glu
                           120
Val Pro Val Trp Pro Leu Pro Ala Lys Lys Ile Cys Val Val Gly Ile
                       135
Ser Gly Leu Met Asp Phe Gln Ala His Leu Ala Ala Ala Ser Leu Arg
                   150
                                       155
Glu Leu Gly Leu Ala Val Glu Thr Ala Glu Ile Glu Leu Pro Glu Leu
               165
                                   170
Asp Val Leu Arg Asn Asn Ala Thr Glu Phe Arg Ala Val Asn Ile Ala
           180
                               185
Arg Phe Leu Asp Asn Glu Glu Asn Trp Pro Leu Leu Leu Asp Ala Leu
       195
                           200
                                               205
Ile Pro Val Ala Asn Thr Cys Glu Met Ile Leu Met Pro Ala Cys Phe
                       215
                                           220
Gly Leu Ala Asp Asp Lys Leu Trp Arg Trp Leu Asn Glu Lys Leu Pro
                  230
                                       235
Cys Ser Leu Met Leu Leu Pro Thr Leu Pro Pro Ser Val Leu Gly Ile
               245
                                  250
Arg Leu Gln Asn Gln Leu Gln Arg Gln Phe Val Arg Gln Gly Gly Val
                               265
           260
Trp Met Pro Gly Asp Glu Val Lys Lys Val Thr Cys Lys Asn Gly Val
                           280
Val Asn Glu Ile Trp Thr Arg Asn His Ala Asp Ile Pro Leu Arg Pro
                       295
                                           300
Arg Phe Ala Val Leu Ala Ser Gly Ser Phe Phe Ser Gly Gly Leu Val
                  310
                                       315
Ala Glu Arg Asn Gly Ile Arg Glu Pro Ile Leu Gly Leu Asp Val Leu
               325
                                   330
Gln Thr Ala Thr Arg Gly Glu Trp Tyr Lys Gly Asp Phe Phe Ala Pro
           340
                               345
Gln Pro Trp Gln Gln Phe Gly Val Thr Thr Asp Glu Thr Leu Arg Pro
                           360
Ser Gln Ala Gly Gln Thr Ile Glu Asn Leu Phe Ala Ile Gly Ser Val
                       375
                                          380
Leu Gly Gly Phe Asp Pro Ile Ala Gln Gly Cys Gly Gly Val Cys
                  390
                                      395
Ala Val Ser Ala Leu His Ala Ala Gln Gln Ile Ala Gln Arg Ala Gly
                                   410
Gly Gln Gln
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<210> 416

<211> 396

<212> PRT

<213> Escherichia coli

<400> 416

Met Asn Asp Thr Ser Phe Glu Asn Cys Ile Lys Cys Thr Val Cys Thr 1 5 10 15

Thr Ala Cys Pro Val Ser Arg Val Asn Pro Gly Tyr Pro Gly Pro Lys 20 25 30

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Gln Ala Gly Pro Asp Gly Glu Arg Leu Arg Leu Lys Asp Gly Ala Leu
Tyr Asp Glu Ala Leu Lys Tyr Cys Ile Asn Cys Lys Arg Cys Glu Val
Ala Cys Pro Ser Asp Val Lys Ile Gly Asp Ile Ile Gln Arg Ala Arg
Ala Lys Tyr Asp Thr Thr Arg Pro Ser Leu Arg Asn Phe Val Leu Ser
His Thr Asp Leu Met Gly Ser Val Ser Thr Pro Phe Ala Pro Ile Val
                              105
           100
Asn Thr Ala Thr Ser Leu Lys Pro Val Arg Gln Leu Leu Asp Ala Ala
                          120
Leu Lys Ile Asp His Arg Arg Thr Leu Pro Lys Tyr Ser Phe Gly Thr
                      135
                                          140
Phe Arg Arg Trp Tyr Arg Ser Val Ala Ala Gln Gln Ala Gln Tyr Lys
                   150
                                      155
Asp Gln Val Ala Phe Phe His Gly Cys Phe Val Asn Tyr Asn His Pro
              165
                                  170
Gln Leu Gly Lys Asp Leu Ile Lys Val Leu Asn Ala Met Gly Thr Gly
                              185
           180
Val Gln Leu Leu Ser Lys Glu Lys Cys Cys Gly Val Pro Leu Ile Ala
       195
                          200
Asn Gly Phe Thr Asp Lys Ala Arg Lys Gln Ala Ile Thr Asn Val Glu
                       215
Ser Ile Arg Glu Ala Val Gly Val Lys Gly Ile Pro Val Ile Ala Thr
                  230
                                      235
Ser Ser Thr Cys Thr Phe Ala Leu Arg Asp Glu Tyr Pro Glu Val Leu
                                   250
Asn Val Asp Asn Lys Gly Leu Arg Asp His Ile Glu Leu Ala Thr Arg
                               265
Trp Leu Trp Arg Lys Leu Asp Glu Gly Lys Thr Leu Pro Leu Lys Pro
                           280
Leu Pro Leu Lys Val Val Tyr His Thr Pro Cys His Met Glu Lys Met
                       295
Gly Trp Thr Leu Tyr Thr Leu Glu Leu Leu Arg Asn Ile Pro Gly Leu
                   310
                                       315
Glu Leu Thr Val Leu Asp Ser Gln Cys Cys Gly Ile Ala Gly Thr Tyr
               325
                                   330
                                                      335
Gly Phe Lys Lys Glu Asn Tyr Pro Thr Ser Gln Ala Ile Gly Ala Pro
                           345
                                                  350
Leu Phe Arg Gln Ile Glu Glu Ser Gly Ala Asp Leu Val Val Thr Asp
                          360
                                              365
Cys Glu Thr Cys Lys Trp Gln Ile Glu Met Ser Thr Ser Leu Arg Cys
                      375
Glu His Pro Ile Thr Leu Leu Ala Gln Ala Leu Ala
                   390
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<210> 417

<211> 302

<212> PRT

<213> Escherichia coli

<400> 417

 Met Gln Leu Arg Lys
 Pro Ala Thr Ala Ile Leu Ala Leu Ala Leu Ser

 1
 5

 Ala Gly Leu Ala Gln Ala Asp Asp Ala Ala Pro Ala Ala Gly Ser Thr

 20
 25

 Leu Asp Lys
 Ile Ala Lys

 Asp Lys
 Ile Ala Lys

 Asp Ser Ser Val
 Pro Phe Ser Tyr Tyr Asp Asn Gln Gln Lys

55 Tyr Ser Gln Asp Tyr Ser Asn Ala Ile Val Glu Ala Val Lys Lys 70 Leu Asn Lys Pro Asp Leu Gln Val Lys Leu Ile Pro Ile Thr Ser Gln 90 Asn Arg Ile Pro Leu Leu Gln Asn Gly Thr Phe Asp Phe Glu Cys Gly 105 Ser Thr Thr Asn Asn Val Glu Arg Gln Lys Gln Ala Ala Phe Ser Asp 120 Thr Ile Phe Val Val Gly Thr Arg Leu Leu Thr Lys Lys Gly Gly Asp 135 Ile Lys Asp Phe Ala Asn Leu Lys Asp Lys Ala Val Val Thr Ser 150 155 Gly Thr Thr Ser Glu Val Leu Leu Asn Lys Leu Asn Glu Glu Gln Lys 165 170 Met Asn Met Arg Ile Ile Ser Ala Lys Asp His Gly Asp Ser Phe Arg 185 Thr Leu Glu Ser Gly Arg Ala Val Ala Phe Met Met Asp Asp Ala Leu 200 Leu Ala Gly Glu Arg Ala Lys Ala Lys Lys Pro Asp Asn Trp Glu Ile 215 Val Gly Lys Pro Gln Ser Gln Glu Ala Tyr Gly Cys Met Leu Arg Lys 230 235 Asp Asp Pro Gln Phe Lys Lys Leu Met Asp Asp Thr Ile Ala Gln Val 245 250 Gln Thr Ser Gly Glu Ala Glu Lys Trp Phe Asp Lys Trp Phe Lys Asn 265 260 Pro Ile Pro Pro Lys Asn Leu Asn Met Asn Phe Glu Leu Ser Asp Glu 280 Met Lys Ala Leu Phe Lys Glu Pro Asn Asp Lys Ala Leu Asn

<210> 418 <211> 328

<212> PRT

<213> Escherichia coli

<400> 418

Met Asn Asn Ser Ala Phe Thr Phe Gln Thr Leu His Pro Asp Thr Ile Met Asp Ala Leu Phe Glu His Gly Ile Arg Val Asp Ser Gly Leu Thr Pro Leu Asn Ser Tyr Glu Asn Arg Val Tyr Gln Phe Gln Asp Glu Asp 40 Arg Arg Arg Phe Val Val Lys Phe Tyr Arg Pro Glu Arg Trp Thr Ala 55 Asp Gln Ile Leu Glu Glu His Gln Phe Ala Leu Gln Leu Val Asn Asp 70 Glu Val Pro Val Ala Ala Pro Val Ala Phe Asn Gly Gln Thr Leu Leu 90 Asn His Gln Gly Phe Tyr Phe Ala Val Phe Pro Ser Val Gly Gly Arg 105 Gln Phe Glu Ala Asp Asn Ile Asp Gln Met Glu Ala Val Gly Arg Tyr 120 Leu Gly Arg Met His Gln Thr Gly Arg Lys Gln Leu Phe Ile His Arg 135 Pro Thr Ile Gly Leu Asn Glu Tyr Leu Ile Glu Pro Arg Lys Leu Phe 155 Glu Asp Ala Thr Leu Ile Pro Ser Gly Leu Lys Ala Ala Phe Leu Lys

```
Ala Thr Asp Glu Leu Ile Ala Ala Val Thr Ala His Trp Arg Glu Asp
         180
               185
Phe Thr Val Leu Arg Leu His Gly Asp Cys His Ala Gly Asn Ile Leu
                 · 200
Trp Arg Asp Gly Pro Met Phe Val Asp Leu Asp Asp Ala Arg Asn Gly
                   215
Pro Ala Val Gln Asp Leu Trp Met Leu Leu Asn Gly Asp Lys Ala Glu
225 230
                                 235
Gln Arg Met Gln Leu Glu Thr Ile Ile Glu Ala Tyr Glu Glu Phe Ser
  , 245
                  . 250
Glu Phe Asp Thr Ala Glu Ile Gly Leu Ile Glu Pro Leu Arg Ala Met
         260
                           265
Arg Leu Val Tyr Tyr Leu Ala Trp Leu Met Arg Arg Trp Ala Asp Pro
           280
Ala Phe Pro Lys Asn Phe Pro Trp Leu Thr Gly Glu Asp Tyr Trp Leu
        295
                                     300
Arg Gln Thr Ala Thr Phe Ile Glu Gln Ala Lys Val Leu Gln Glu Pro
                                 315
    310
Pro Leu Gln Leu Thr Pro Met Tyr
             325
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<210> 419 <211> 208

<212> PRT

<213> Escherichia coli

<400> 419

Met Lys Lys Ile Trp Leu Ala Leu Ala Gly Leu Val Leu Ala Phe Ser 10 Ala Ser Ala Ala Gln Tyr Glu Asp Gly Lys Gln Tyr Thr Thr Leu Glu 25 Lys Pro Val Ala Gly Ala Pro Gln Val Leu Glu Phe Phe Ser Phe Phe 40 Cys Pro His Cys Tyr Gln Phe Glu Glu Val Leu His Ile Ser Asp Asn 55 Val Lys Lys Lys Leu Pro Glu Gly Val Lys Met Thr Lys Tyr His Val 75 70 Asn Phe Met Gly Gly Asp Leu Gly Lys Asp Leu Thr Gln Ala Trp Ala 90 85 Val Ala Met Ala Leu Gly Val Glu Asp Lys Val Thr Val Pro Leu Phe 105 110 100 Glu Gly Val Gln Lys Thr Gln Thr Ile Arg Ser Ala Ser Asp Ile Arg 125 120 Asp Val Phe Ile Asn Ala Gly Ile Lys Gly Glu Glu Tyr Asp Ala Ala 130 135 Trp Asn Ser Phe Val Val Lys Ser Leu Val Ala Gln Gln Glu Lys Ala **150** . Ala Ala Asp Val Gln Leu Arg Gly Val Pro Ala Met Phe Val Asn Gly 165 170 Lys Tyr Gln Leu Asn Pro Gln Gly Met Asp Thr Ser Asn Met Asp Val 185 Phe Val Gln Gln Tyr Ala Asp Thr Val Lys Tyr Leu Ser Glu Lys Lys 200

<210> 420

<211> 112

<212> PRT

<213> Escherichia coli

<210> 421 <211> 346

<212> PRT

<213> Escherichia coli

<400> 421

Met Lys Ser Val Val Asn Asp Thr Asp Gly Ile Val Arg Val Ala Glu Ser Val Ile Pro Glu Ile Lys His Gln Asp Glu Val Arg Val Lys Ile Ala Ser Ser Gly Leu Cys Gly Ser Asp Leu Pro Arg Ile Phe Lys Asn 40 Gly Ala His Tyr Tyr Pro Ile Thr Leu Gly His Glu Phe Ser Gly Tyr 55 Ile Asp Ala Val Gly Ser Gly Val Asp Asp Leu His Pro Gly Asp Ala 70 75 Val Ala Cys Val Pro Leu Leu Pro Cys Phe Thr Cys Pro Glu Cys Leu 90 Lys Gly Phe Tyr Ser Gln Cys Ala Lys Tyr Asp Phe Ile Gly Ser Arg 100 105 Arg Asp Gly Gly Phe Ala Glu Tyr Ile Val Val Lys Arg Lys Asn Val 120 Phe Ala Leu Pro Thr Asp Met Pro Ile Glu Asp Gly Ala Phe Ile Glu 135 Pro Ile Thr Val Gly Leu His Ala Phe His Leu Ala Gln Gly Cys Glu 155 150 Asn Lys Asn Val Ile Ile Ile Gly Ala Gly Thr Ile Gly Leu Leu Ala 165 170 Ile Gln Cys Ala Val Ala Leu Gly Ala Lys Ser Val Thr Ala Ile Asp 185 Ile Ser Ser Glu Lys Leu Ala Leu Ala Lys Ser Phe Gly Ala Met Gln 200 Thr Phe Asn Ser Ser Glu Met Ser Ala Pro Gln Met Gln Ser Val Leu 215 220 Arg Glu Leu Arg Phe Asn Gln Leu Ile Leu Glu Thr Ala Gly Val Pro 230 235 Gln Thr Val Glu Leu Ala Val Glu Ile Ala Gly Pro His Ala Gln Leu 245 Ala Leu Val Gly Thr Leu His Gln Asp Leu His Leu Thr Ser Ala Thr 265 Phe Gly Lys Ile Leu Arg Lys Glu Leu Thr Val Ile Gly Ser Trp Met 280 Asn Tyr Ser Ser Pro Trp Pro Gly Gln Glu Trp Glu Thr Ala Ser Arg 295 290

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Leu Leu Thr Glu Arg Lys Leu Ser Leu Glu Pro Leu Ile Ala His Arg 315 310 Gly Ser Phe Glu Ser Phe Ala Gln Ala Val Arg Asp Ile Ala Arg Asn 330 Ala Met Pro Gly Lys Val Leu Leu Ile Pro

<210> 422 <211> 451 <212> PRT <213> Escherichia coli

<400> 422

Met Phe Ser Glu Val Met Arg Tyr Ile Leu Asp Leu Gly Pro Thr Val 10 Met Leu Pro Ile Val Ile Ile Ile Phe Ser Lys Ile Leu Gly Met Lys 25 Ala Gly Asp Cys Phe Lys Ala Gly Leu His Ile Gly Ile Gly Phe Val 40 Gly Ile Gly Leu Val Ile Gly Leu Met Leu Asp Ser Ile Gly Pro Ala Ala Lys Ala Met Ala Glu Asn Phe Asp Leu Asn Leu His Val Val Asp 75 .70 Val Gly Trp Pro Gly Ser Ser Pro Met Thr Trp Ala Ser Gln Ile Ala 90 Leu Val Ala Ile Pro Ile Ala Ile Leu Val Asn Val Ala Met Leu Leu 105 Thr Arg Met Thr Arg Val Val Asn Val Asp Ile Trp Asn Ile Trp His 125 120 Met Thr Phe Thr Gly Ala Leu Leu His Leu Ala Thr Gly Ser Trp Met 135 140 Ile Gly Met Ala Gly Val Val Ile His Ala Ala Phe Val Tyr Lys Leu 150 155 Gly Asp Trp Phe Ala Arg Asp Thr Arg Asn Phe Phe Glu Leu Glu Gly 170 165 Ile Ala Ile Pro His Gly Thr Ser Ala Tyr Met Gly Pro Ile Ala Val 185 Leu Val Asp Ala Ile Ile Glu Lys Ile Pro Gly Val Asn Arg Ile Lys 200 Phe Ser Ala Asp Asp Ile Gln Arg Lys Phe Gly Pro Phe Gly Glu Pro 215 220 Val Thr Val Gly Phe Val Met Gly Leu Ile Ile Gly Ile Leu Ala Gly 230 235 Tyr Asp Val Lys Gly Val Leu Gln Leu Ala Val Lys Thr Ala Ala Val 250 Met Leu Leu Met Pro Arg Val Ile Lys Pro Ile Met Asp Gly Leu Thr 265 Pro Ile Ala Lys Gln Ala Arg Ser Arg Leu Gln Ala Lys Phe Gly Gly 280 Gln Glu Phe Leu Ile Gly Leu Asp Pro Ala Leu Leu Gly His Thr 300 -295 Ala Val Val Ser Ala Ser Leu Ile Phe Ile Pro Leu Thr Ile Leu Ile 310 315 Ala Val Cys Val Pro Gly Asn Gln Val Leu Pro Phe Gly Asp Leu Ala 325 330 Thr Ile Gly Phe Phe Val Ala Met Ala Val Ala Val His Arg Gly Asn 345 Leu Phe Arg Thr Leu Ile Ser Gly Val Ile Ile Met Ser Ile Thr Leu 365 360 Trp Ile Ala Thr Gln Thr Ile Gly Leu His Thr Gln Leu Ala Ala Asn PCT/US00/34419

WO 01/48209 375 380 Ala Gly Ala Leu Lys Ala Gly Gly Met Val Ala Ser Met Asp Gln Gly 390 395 Gly Ser Pro Ile Thr Trp Leu Leu Ile Gln Val Phe Ser Pro Gln Asn 405 410 Ile Pro Gly Phe Ile Ile Gly Ala Ile Tyr Leu Thr Gly Ile Phe 420 425 Met Thr Trp Arg Arg Ala Arg Gly Phe Ile Lys Gln Glu Lys Val Val 435 440 Leu Ala Glu 450 <210> 423 <211> 94 <212> PRT <213> Escherichia coli <400> 423 Met Lys Arg Lys Ile Ile Val Ala Cys Gly Gly Ala Val Ala Thr Ser Thr Met Ala Ala Glu Glu Ile Lys Glu Leu Cys Gln Asn His Asn Ile 25 Pro Val Glu Leu Ile Gln Cys Arg Val Asn Glu Ile Glu Thr Tyr Met 40 Asp Gly Val His Leu Ile Cys Thr Thr Ala Lys Val Asp Arg Ser Phe 55 Gly Asp Ile Pro Leu Val His Gly Met Pro Phe Ile Ser Gly Ile Gly 70 Ile Glu Ala Leu Gln Asn Lys Ile Leu Thr Ile Leu Gln Gly <210> 424 <211> 150 <212> PRT <213> Escherichia coli Met Thr Asn Leu Phe Val Arg Ser Gly Ile Ser Phe Val Asp Arg Ser Glu Val Leu Thr His Ile Gly Asn Glu Met Leu Ala Lys Gly Val Val 25 His Asp Thr Trp Pro Gln Ala Leu Ile Ala Arq Glu Ala Glu Phe Pro 40

Thr Gly Ile Met Leu Glu Gln His Ala Ile Ala Ile Pro His Cys Glu 55 Ala Ile His Ala Lys Ser Ser Ala Ile Tyr Leu Leu Arg Pro Thr Asn 70 75 Lys Val His Phe Gln Gln Ala Asp Asp Asp Asn Asp Val Ala Val Ser 90 Leu Val Ile Ala Leu Ile Val Glu Asn Pro Gln Gln Leu Lys Leu 105 Leu Arg Cys Leu Phe Gly Lys Leu Gln Gln Pro Asp Ile Val Glu Thr 120 Leu Ile Thr Leu Pro Glu Thr Gln Leu Lys Glu Tyr Phe Thr Lys Tyr 135 Val Leu Asp Ser Asp Glu 150

<210> 425 <211> 420 <212> PRT <213> Escherichia coli <400> 425 Met Lys Thr Leu Ile Ala Arg His Lys Ala Gly Glu His Ile Gly Ile Cys Ser Val Cys Ser Ala His Pro Leu Val Ile Glu Ala Ala Leu Ala Phe Asp Arg Asn Ser Thr Arg Lys Val Leu Ile Glu Ala Thr Ser Asn 40 Gln Val Asn Gln Phe Gly Gly Tyr Thr Gly Met Thr Pro Ala Asp Phe Arg Glu Phe Val Phe Thr Ile Ala Asp Lys Val Gly Phe Ala Arg Glu 75 Arg Ile Ile Leu Gly Gly Asp His Leu Gly Pro Asn Cys Trp Gln Gln Glu Asn Ala Asp Ala Ala Met Glu Lys Ser Val Glu Leu Val Lys Glu 105 110 Tyr Val Arg Ala Gly Phe Ser Lys Ile His Leu Asp Ala Ser Met Ser 125 120 Cys Ala Gly Asp Pro Ile Pro Leu Ala Pro Glu Thr Val Ala Glu Arg . 135 140 Ala Ala Val Leu Cys Phe Ala Ala Glu Ser Val Ala Thr Asp Cys Gln 150 155 Arg Glu Gln Leu Ser Tyr Val Ile Gly Thr Glu Val Pro Val Pro Gly 170 Gly Glu Ala Ser Ala Ile Gln Ser Val His Ile Thr His Val Glu Asp 185 Ala Ala Asn Thr Leu Arg Thr His Gln Lys Ala Phe Ile Ala Arg Gly 200 Leu Thr Glu Ala Leu Thr Arg Val Ile Ala Ile Val Val Gln Pro Gly 210 215 Val Glu Phe Asp His Ser Asn Ile Ile His Tyr Gln Pro Gln Glu Ala 230 235 Gln Pro Leu Ala Gln Trp Ile Glu Asn Thr Arg Met Val Tyr Glu Ala 245 250 His Ser Thr Asp Tyr Gln Thr Arg Thr Ala Tyr Trp Glu Leu Val Arg 265 Asp His Phe Ala Ile Leu Lys Val Gly Pro Ala Leu Thr Phe Ala Leu 280 Arg Glu Ala Ile Phe Ala Leu Ala Gln Ile Glu Gln Glu Leu Ile Ala 295 Pro Glu Asn Arg Ser Gly Cys Leu Ala Val Ile Glu Glu Val Met Leu 310 315 Asp Glu Pro Gln Tyr Trp Lys Lys Tyr Tyr Arg Thr Gly Phe Asn Asp 325 330 · Ser Leu Leu Asp Ile Arg Tyr Ser Leu Ser Asp Arg Ile Arg Tyr Tyr 340 345 Trp Pro His | Ser Arg Ile Lys Asn Ser Val Glu Thr Met Met Val Asn 360 Leu Glu Gly Val Asp Ile Pro Leu Gly Met Ile Ser Gln Tyr Leu Pro . 375 Lys Gln Phe Glu Arg Ile Gln Ser Gly Glu Leu Ser Ala Ile Pro His 395 390. Gln Leu Ile Met Asp Lys Ile Tyr Asp Val Leu Arg Ala Tyr Arg Tyr Gly Cys Ala Glu 420

<210> 426 <211> 286

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<212> PRT
<213> Escherichia coli
<400> 426
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Arg Gly Gly Tyr Ala Val Pro Ala Phe Asn Ile His Asn Leu Glu Thr
                               25
Met Gln Val Val Val Glu Thr Ala Ala Asn Leu His Ala Pro Val Ile
                            40
Ile Ala Gly Thr Pro Gly Thr Phe Thr His Ala Gly Thr Glu Asn Leu
                       55
Leu Ala Leu Val Ser Ala Met Ala Lys Gln Tyr His His Pro Leu Ala
                   70
                                       75
Ile His Leu Asp His His Thr Lys Phe Asp Asp Ile Ala Gln Lys Val
               85
                                   90
Arg Ser Gly Val Arg Ser Val Met Ile Asp Ala Ser His Leu Pro Phe
                               105
                                                   110
Ala Gln Asn Ile Ser Arg Val Lys Glu Val Val Asp Phe Cys His Arg
                          120
Phe Asp Val Ser Val Glu Ala Glu Leu Gly Gln Leu Gly Gly Gln Glu
                       135
Asp Asp Val Gln Val Asn Glu Ala Asp Ala Leu Tyr Thr Asn Pro Ala
                   150
                                       155
Gln Ala Arg Glu Phe Ala Glu Ala Thr Gly Ile Asp Ser Leu Ala Val
               165
                                   170
Ala Ile Gly Thr Ala His Gly Met Tyr Ala Ser Ala Pro Ala Leu Asp
                               185
Phe Ser Arg Leu Glu Asn Ile Arg Gln Trp Val Asn Leu Pro Leu Val
                           200
Leu His Gly Ala Ser Gly Leu Ser Thr Lys Asp Ile Gln Gln Thr Ile
                      215
Lys Leu Gly Ile Cys Lys Ile Asn Val Ala Thr Glu Leu Lys Asn Ala
                   230
                                       235
Phe Ser Gln Ala Leu Lys Asn Tyr Leu Thr Glu His Pro Glu Ala Thr
                                   250
Asp Pro Arg Asp Tyr Leu Gln Ser Ala Lys Ser Ala Met Arg Asp Val
                              265
Val Ser Lys Val Ile Ala Asp Cys Gly Cys Glu Gly Arg Ala
<210> 427
<211> 157
<212> PRT
<213> Escherichia coli
<400> 427
Met Ser Gln Asn Asp Ile Ile Ile Arg Thr His Tyr Lys Ser Pro His
                                   10
Arg Leu His Ile Asp Ser Asp Ile Pro Thr Pro Ser Ser Glu Pro Ile
                               25
Asn Gln Phe Ala Arg Gln Leu Ile Thr Leu Leu Asp Thr Ser Asp Leu
                           40
Ser Ser Met Leu Ser Tyr Cys Val Thr Gln Glu Phe Thr Ala Asn Cys
                       55
Arg Lys Ile Ser Gln Asn Cys Tyr Ser Thr Ala Leu Phe Thr Ile Asn
```

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Phe Ala Thr Ser Pro Ile His Thr Glu Asn Ile Leu Ile Thr Leu His 85 90 Tyr Lys Lys Glu Ile Ile Ser Leu Leu Leu Glu Thr Thr Pro Ile Lys 105 Ala Asn His Leu Arg Ser Ile Leu Asp Tyr Ile Glu Gln Glu Gln Leu 120 Thr Ala Glu Asp Arg Asn His Cys Met Lys Leu Ser Lys Lys Ile His 140 135 Arg Glu Lys Asn Tyr Thr Pro Asn Ser Lys Ser Gln Trp 150

<210> 428 <211> 471 <212> PRT <213> Escherichia coli

<400> 428 Met Gln Ser Pro Ser Asp Ala Ile Phe Cys Arg His Leu Ser Leu Gln 10 Tyr Ala Leu Asp Ser Leu Arg Asn Gly Lys Gly Lys Val Asn Leu Ile 25 Lys His Tyr Ser Ser Val Glu Ser Ile Gln Gln His Val Pro Leu Val 40 Arg Asp Ala Glu Phe Arg Ala Leu Leu Arg His Pro Pro Ala Gly Ser 55 Arg Val Ile Ala Ser Lys Asp Phe Gly Phe Ala Leu Asp Ile Phe Phe 75 70 Cys Arg Met Met Ala Asn Asn Val Ser His Met Ser Ala Ile Leu Tyr 90 . 85 Ile Asp Asn His Thr Leu Ser Val Arg Leu Arg Ile Lys Gln Ser Val 105 100 Tyr Gly Gln Leu Asn Tyr Val Val Ser Val Tyr Asp Pro Asn Asp Thr 120 Asn Val Ala Val Arg Asp Thr His Arg Thr Ala Arg Gly Phe Leu Ser 135 140 Leu Asp Lys Phe Ile Ser Ser Gly Pro Asp Ala Gln Thr Trp Ala Asp 150 155 Arg Tyr Val Arg Asn Cys Ala Ile Ala Ile Leu Pro Leu Leu Pro Val 165 170 175 Gly Val Pro Gly Ala Ile Phe Ala Gly Ile Ala Ser Arg Met Pro Phe 180 185 Ala Pro Ile His Pro Ser Ala Met Leu Leu Ile Met Ala Thr Gly Gln 200 Ser Gln Gln Leu Ile Thr Leu Phe Lys Gln Leu Pro Ile Leu Pro Glu 215 220 Lys Glu Ile Ile Glu Ile Ile Thr Ala Gln Asn Ser Val Gly Thr Pro 235 230 Ala Leu Phe Leu Ala Met Met Asn Gly His Thr Asp Asn Val Lys Ile 250 245 Phe Met Gln Glu Ile Gln Ser Leu Val Asp Asn His Ile Ile His Glu 265 260 Asp Asn Leu Val Lys Leu Leu Gln Thr Lys Ser Ala Asn Glu Thr Pro 275 . 280 Gly Leu Tyr Ile Ser Met Leu Tyr Gly Phe Asp Glu Ile Ile Asp Ile 295 Phe Leu Asn Ala Leu Thr Thr Pro Ile Ala Gln Glu Leu Leu Asn Lys 315 305 310 Lys Leu Val Met Ser Ile Leu Ala Met Lys Ile His Asp Gly Glu Pro 330 325 Gly Leu Tyr Ala Ala Met Glu Asn Asn His Pro Leu Cys Val Thr Arg

```
345
Phe Leu Ser Lys Ile Asn Gly Ile Ala Phe Lys Tyr Lys Leu Ser Lys
                            360
                                                365
Ala Asn Ile Met Asp Leu Leu Lys Gly Ala Thr Ala Gln Gly Thr Pro
                       375
                                            380
Ala Leu Tyr Ile Ala Met Ser Lys Gly Asn Glu Asp Val Val Leu Ser
                   390
                                       395
Tyr Ile Ser Thr Leu Gly Ala Phe Ala Lys Lys His Ser Phe Ser Gln
                405
                                   410
His Gln Leu Phe Thr Leu Leu Ala Ala Lys Asn His Asp Asn Met Ser
                                425
           420
Ala Val His Ile Ala Ile His His Lys His Tyr Lys Thr Val Glu Thr
                           440
                                              445
Tyr Tyr Ala Ala Ile Asn Ala Ile Ser Gln Ser Leu Ser Phe Ser Ala
                      455
Asp Glu Ile Lys Thr Tyr Leu
                    470
<210> 429
<211> 128
<212> PRT
<213> Escherichia coli
<400> 429
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 Met
 Pro
 Ser
 Gly
 Leu
 Phe
 Met
 Asp
 Leu
 Leu
 Pro
 Phe
 Leu
 Pro
 Phe
 Leu
 Pro
 Phe
 Phe</th

<210> 430 <211> 398 <212> PRT <213> Escherichia coli

<400> 430

 Met
 Lys
 Thr
 Trp
 Ile
 Phe
 Ile
 Cys
 Met
 Ser
 Ile
 Ala
 Met
 Leu
 Leu
 Leu
 Trp

 Phe
 Leu
 Ser
 Thr
 Leu
 Arg
 Arg
 Lys
 Pro
 Ser
 Gln
 Lys
 Lys
 Gly
 Cys
 Ile

 Asp
 Ala
 Ile
 Pro
 Ala
 Tyr
 Asp
 Gly
 Pro
 Cys
 Leu
 Ala
 Gln
 Ser

 Leu
 Asp
 Asp
 Leu
 Arg
 Asp
 Pro
 Tyr
 Phe
 Cys
 Arg
 Val
 Ile
 Cys
 Ile
 Ala
 Gln
 Ser
 Ala
 Gln
 Ser
 Arg
 Val
 Ala
 Fro
 Tyr
 Phe
 Cys
 Arg
 Val
 Ile
 Cys
 Val
 Ala
 Ile
 Cys
 Val
 Ala
 Ile
 Cys
 Val
 Ala
 Ile
 Cys
 Arg
 Val
 Ala

```
Lys Gly Gly Ala Leu Met Asn Gly Leu Asn Tyr Ala Thr Cys Asp Gln
                . 105
          100
Val Phe Leu Ser Asp Ala Asp Thr Tyr Val Pro Pro Asp Gln Asp Gly
                        120
Met Gly Tyr Met Leu Ala Glu Ile Glu Arg Gly Ala Asp Ala Val Gly
                    135
Gly Ile Pro Ser Thr Ala Leu Lys Gly Ala Gly Leu Leu Pro His Ile
                150
                                  155
Arg Ala Thr Val Lys Leu Pro Met Ile Val Met Lys Arg Thr Leu Gln
                   170
Gln Leu Leu Gly Gly Ala Pro Phe Ile Ile Ser Gly Ala Cys Gly Met
                . 185
         180
Phe Arg Thr Asp Val Leu Arg Lys Phe Gly Phe Ser Asp Arg Thr Lys
                        200
Val Glu Asp Leu Asp Leu Thr Trp Thr Leu Val Ala Asn Gly Tyr Arg
                                      220
                    215
Ile Arg Gln Ala Asn Arg Cys Ile Val Tyr Pro Gln Glu Cys Asn Ser
                                  235
                230
Pro Arg Glu Glu Trp Arg Arg Trp Arg Trp Ile Val Gly Tyr Ala
                              250
              245
Val Cys Met Arg Leu His Lys Arg Leu Leu Phe Ser Arg Phe Gly Ile
                            265
          260
Phe Ser Ile Phe Pro Met Leu Leu Val Val Leu Tyr Gly Val Gly Ile
   275 280
Tyr Leu Thr Thr Trp Phe Asn Glu Phe Ile Thr Thr Gly Pro His Gly
        295
                                      300
Val Val Leu Ala Met Phe Pro Leu Ile Trp Val Gly Val Val Cys Val
                                  315
                 310
Ile Gly Ala Phe Ser Ala Trp Phe His Arg Cys Trp Leu Leu Val Pro
             325
                              330
Leu Ala Pro Leu Ser Val Val Tyr Val Leu Leu Ala Tyr Ala Ile Trp
          340
                           345
Ile Ile Tyr Gly Leu Ile Ala Phe Phe Thr Gly Arg Glu Pro Gln Arg
                        360
Asp Lys Pro Thr Arg Tyr Ser Ala Leu Val Glu Ala Ser Thr Ala Tyr
                   375
Ser Gln Pro Ser Val Thr Gly Thr Glu Lys Leu Ser Glu Ala
               390 . 395
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<210> 431 <211> 552

<212> PRT

<213> Escherichia coli

<400> 431

Met Ile Leu Glu Arg Val Glu Ile Val Gly Phe Arg Gly Ile Asn Arg 10 Leu Ser Leu Met Leu Glu Gln Asn Asn Val Leu Ile Gly Glu Asn Ala 25 20 Trp Gly Lys Ser Ser Leu Leu Asp Ala Leu Thr Leu Leu Leu Ser Pro 40 Glu Ser Asp Leu Tyr His Phe Glu Arg Asp Asp Phe Trp Phe Pro Pro 55 Gly Asp Ile Asn Gly Arg Glu His His Leu His Ile Ile Leu Thr Phe 70 Arg Glu Ser Leu Pro Gly Arg His Arg Val Arg Arg Tyr Arg Pro Leu 90 85 Glu Ala Cys Trp Thr Pro Cys Thr Asp Gly Tyr His Arg Ile Phe Tyr 105 100 Arg Leu Glu Gly Glu Ser Ala Glu Asp Gly Ser Val Met Thr Leu Arg

```
120
Ser Phe Leu Asp Lys Asp Gly His Pro Ile Asp Val Glu Asp Ile Asn
                       135
                                          140
Asp Gln Ala Arg His Leu Val Arg Leu Met Pro Val Leu Arg Leu Arg
                   150
                                       155
Asp Ala Arg Phe Met Arg Arg Ile Arg Asn Gly Thr Val Pro Asn Val
               165
                                   170
Pro Asn Val Glu Val Thr Ala Arg Gln Leu Asp Phe Leu Ala Arg Glu
                               185
Leu Ser Ser His Pro Gln Asn Leu Ser Asp Gly Gln Ile Arg Gln Gly
                           200
Leu Ser Ala Met Val Gln Leu Leu Glu His Tyr Phe Ser Glu Gln Gly
                       215
Ala Gly Gln Ala Arg Tyr Arg Leu Met Arg Arg Arg Ala Ser Asn Glu
                   230
                                       235
Gln Arg Ser Trp Arg Tyr Leu Asp Ile Ile Asn Arg Met Ile Asp Arg
                                   250
Pro Gly Gly Arg Ser Tyr Arg Val Ile Leu Leu Gly Leu Phe Ala Thr
                               265
Leu Leu Gln Ala Lys Gly Thr Leu Arg Leu Asp Lys Asp Ala Arg Pro
                           280
Leu Leu Ile Glu Asp Pro Glu Thr Arg Leu His Pro Ile Met Leu
                       295
                                           300
Ser Val Ala Trp His Leu Leu Asn Leu Leu Pro Leu Gln Arg Ile Ala
                   310
                                       315
Thr Thr Asn Ser Gly Glu Leu Leu Ser Leu Thr Pro Val Glu His Val
                                  330
Cys Arg Leu Val Arg Glu Ser Ser Arg Val Ala Ala Trp Arg Leu Gly
                              345
Pro Ser Gly Leu Ser Thr Glu Asp Ser Arg Arg Ile Ser Phe His Ile
                           360
Arg Phe Asn Arg Pro Ser Ser Leu Phe Ala Arg Cys Trp Leu Leu Val
                       375
                                           380
Glu Gly Glu Thr Glu Thr Trp Val Ile Asn Glu Leu Ala Arg Gln Cys
                   390
                                       395
Gly His His Phe Asp Ala Glu Gly Ile Lys Val Ile Glu Phe Ala Gln
              405
                                  410
Ser Gly Leu Lys Pro Leu Val Lys Phe Ala Arg Arg Met Gly Ile Glu
                               425
           420
Trp His Val Leu Val Asp Gly Asp Glu Ala Gly Lys Lys Tyr Ala Ala
                           440
Thr Val Arg Ser Leu Leu Asn Asn Asp Arg Glu Ala Glu Arg Glu His
                       455
Leu Thr Ala Leu Pro Ala Leu Asp Met Glu His Phe Met Tyr Arg Gln
                   470
                                       475
Gly Phe Ser Asp Val Phe His Arg Met Ala Gln Ile Pro Glu Asn Val
               485
                                   490
Pro Met Asn Leu Arg Lys Ile Ile Ser Lys Ala Ile His Arg Ser Ser
                               505
Lys Pro Asp Leu Ala Ile Glu Val Ala Met Glu Ala Gly Arg Arg Gly
                           520
Val Asp Ser Val Pro Thr Leu Leu Lys Lys Met Phe Ser Arg Val Leu
                       535
Trp Leu Ala Arg Gly Arg Ala Asp
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<210> 432

<211> 352

<212> PRT

<213> Escherichia coli

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<400> 432
Met Leu Pro Ser Ile Ser Ile Asn Asn Thr Ser Ala Ala Tyr Pro Glu
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Ser Ile Asn Glu Asn Asn Asn Asp Glu Val Asn Gly Leu Val Gln Glu
      20
Phe Lys Asn Leu Phe Asn Gly Lys Glu Gly Ile Ser Thr Cys Ile Lys
                       40
His Leu Leu Glu Leu Ile Lys Asn Ala Ile Arg Val Asn Asp Asp Pro
                   55
Tyr Arg Phe Asn Ile Asn Asn Ser Ser Val Thr Tyr Ile Asp Ile Asp
              70
Ser Asn Asp Thr Asp His Ile Thr Ile Gly Ile Asp Asn Gln Glu Pro
                              90
            85
Ile Glu Leu Pro Ala Asn Tyr Lys Asp Lys Glu Leu Val Arg Thr Ile
                           105
         100
Ile Asn Asp Asn Ile Val Glu Lys Thr His Asp Ile Asn Asn Lys Glu
                       120
Met Ile Phe Ser Ala Leu Lys Glu Ile Tyr Asp Gly Asp Pro Gly Phe
                   135
                            . 140
Ile Phe Asp Lys Ile Ser His Lys Leu Arg His Thr Val Thr Glu Phe
                           155
                150
Asp Glu Ser Gly Lys Ser Glu Pro Thr Asp Leu Phe Thr Trp Tyr Gly
             165 170 175
Lys Asp Lys Lys Gly Asp Ser Leu Ala Ile Val Ile Lys Asn Lys Asn
                  185 - 190
Gly Asn Asp Tyr Leu Ser Leu Gly Tyr Tyr Asp Gln Asp Asp Tyr His
                200
Ile Gln Arg Gly Ile Arg Ile Asn Gly Asp Ser Leu Thr Gln Tyr Cys
                                     220
                   215
Ser Glu Asn Ala Arg Ser Ala Ser Ala Trp Phe Glu Ser Ser Lys Ala
                                  235
                230
Ile Met Ala Glu Ser Phe Ala Thr Gly Ser Asp His Gln Val Val Asn
                              250
             245
Glu Leu Asn Gly Glu Arg Leu Arg Glu Pro Asn Asp Val Phe Lys Arg
                           265 270
Tyr Gly Arg Ala Ile Arg Tyr Asp Phe Gln Val Asp Asp Ala Lys Tyr
     275 280
Lys Cys Asp His Leu Lys Glu Ile Val Ser Thr Leu Val Gly Asn Lys
                   295
Ile Asn Val Gly His Ser Gln Lys Ile Tyr Lys His Phe Lys Asp Leu
                310
                                  315
Glu Gly Lys Ile Glu Glu Arg Leu Gln Asn Arg Gln Ala Glu Tyr Gln
                              330
Asn Glu Ile Asn Gln Pro Ser Ala Pro Gly Val Asn Phe Asp Asp Ile
                                             350
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```
<210> 433
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<400> 433

 Met
 Met
 Arg
 His
 Leu
 Arg
 Asn
 Ile
 Phe
 Asn
 Leu
 Gly
 Ile
 Leu
 Ile
 Leu
 Ile
 Leu
 Ile
 Val
 Phe
 Ser

 Arg
 Ser
 Leu
 Leu
 Gly
 Asp
 Lys
 Ala
 Met
 Leu
 Thr
 Leu
 Ile
 Val
 Phe
 Ser

 Phe
 Thr
 Val
 Ser
 Val
 Thr
 Val
 Thr
 Pro
 Gly
 Ser
 Leu

 Asn
 Leu
 Ala
 Pro
 Ile
 Ala
 Ile
 Ala
 Asp
 Met
 Asp
 Gln
 Ser
 Gln
 Leu
 Ser

<211> 375

<212> PRT

<213> Escherichia coli

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55
Asn Arg Ile Val Asn Ser Phe Tyr Arg Pro Trp Phe Leu Pro Pro Glu
                  70
Met Ile Thr Ala Asp Glu Met Asp Ala Gly Leu Asp Ala Gly Arg Tyr
                                  90
Thr Phe Ala Ile Asn Ile Pro Pro Asn Phe Gln Arg Asp Val Leu Ala
                              105
Gly Arg Gln Pro Asp Ile Gln Val Asn Val Asp Ala Thr Arg Met Ser
                          120
Gln Ala Phe Thr Gly Asn Gly Tyr Ile Gln Asn Ile Ile Asn Gly Glu
                      135
Val Asn Ser Phe Val Ala Arg Tyr Arg Asp Asn Ser Glu Pro Leu Val
                                      155
Ser Leu Glu Thr Arg Met Arg Phe Asn Pro Asn Leu Asp Pro Ala Trp
                                  170
Phe Gly Gly Val Met Ala Ile Ile Asn Asn Ile Thr Met Leu Ala Ile
                               185
Val Leu Thr Gly Ser Ala Leu Ile Arg Glu Arg Glu His Gly Thr Val
                          200
Glu His Leu Leu Val Met Pro Ile Thr Pro Phe Glu Ile Met Met Ala
                      215
                                          220
Lys Ile Trp Ser Met Gly Leu Val Val Leu Val Val Ser Gly Leu Ser
                  230
                                      235
Leu Val Leu Met Val Lys Gly Val Leu Gly Val Pro Ile Glu Gly Ser
                                 250
Ile Pro Leu Phe Met Leu Gly Val Ala Leu Ser Leu Phe Ala Thr Thr
                              265
Ser Ile Gly Ile Phe Met Gly Thr Ile Ala Arg Ser Met Pro Gln Leu
                          280
Gly Leu Leu Val Ile Leu Val Leu Leu Pro Leu Gln Met Leu Ser Gly
                      295
                                       300
Gly Ser Thr Pro Arg Glu Ser Met Pro Gln Met Val Gln Asp Ile Met
                   310
                                       315
Leu Thr Met Pro Thr Thr His Phe Val Ser Leu Ala Gln Ala Ile Leu
                                   330
Tyr Arg Gly Ala Gly Phe Glu Ile Val Trp Pro Gln Phe Leu Thr Leu
                               345
Met Ala Ile Gly Gly Ala Phe Phe Thr Ile Ala Leu Leu Arg Phe Arg
                           360
Lys Thr Ile Gly Thr Met Ala
    370
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<210> 434

<211> 894

<212> PRT

<213> Escherichia coli

<400> 434

 Met Ser Gln His Tyr Gly Lys Thr Val Ala Leu Asn Asn Ile Thr Leu

 1
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 Asp Ile Pro Ala Arg Cys Met Val Gly Leu Ile Gly Pro Asp Gly Val

 20
 25

 30

 Gly Lys Ser Ser Leu Leu Ser Leu Ile Ser Gly Ala Arg Val Ile Glu

 35
 40

 40
 45

 Gln Gly Asn Val Met Val Leu Gly Gly Asp Met Arg Asp Pro Lys His

 50
 55

 Arg Arg Asp Val Cys Pro Arg Ile Ala Trp Met Pro Gln Gly Leu Gly

 65
 70

 Lys Asn Leu Tyr His Thr Leu Ser Val Tyr Glu Asn Val Asp Phe Phe

 90

Ala	Arg	Leu	Phe 100	Gly	His	Asp	ГÀЗ	Ala 105	Glu	Arg	Glu	Val	Arg 110	Ile	Asn
Glu	Leu	Leu 115		Ser	Thr	Gly	Leu 120	Ala	Pro	Phe	Arg	Asp 125	Arg	Pro	Ala
Gly	Lys 130		Ser	Gly	Gly	Met 135	Lys	Gln	Lys	Leu	Gly 140	Leu	Суз	Cys	Ala
Leu 145		His	Asp	Pro	Glu 150		Leu	Ile	Leu	Asp 155	Glu	Pro	Thr	Thr	Gly 160
	Asp	Pro	Leu	Ser 165		Ser	Gln	Phe	Trp 170	Asp	Leu	Ile	Asp	Ser 175	Ile
Arg	Gln	Arg	Gln 180		Asn	Met	Ser	Val 185	Leu	Val	Ala	Thr	Ala 190	Tyr	Met
Glu	Glu	Ala 195	Glu	Arg	Phe	Asp	Trp 200	Leu	Val	Ala	Met	Asn 205	Ala	Gly	Glu
Val	Leu 210	Ala	Thr	Gly	Ser	Ala 215	Glu	Glu	Leu	Arg	Gln 220	Gln	Thr	Gln	Ser
225					230					235			Ala		240
				245					250				Glu	255	
			260			•		265					Gly 270		
		275					280					285	Glu		
_	290					295					300		Met		-
305		_			310				_	315		_	Leu		320
				325					330				Val	335	
			340					345					Arg 350		
		355			_		360					365	Glu		
	370					375					380		Asp		
385					390	•				395			Arg		400
				405					410				Leu	415	
			420					425					Trp		
· .		435					440					445			
	450					455					460		Leu		
465					470					475			Val Leu		480
_	_			485	. •				490				Val	495	
			500					505	•				510 Leu		•
		515					520					525			
_	530	_	_			535					540				Tyr
545					550					555					560 Arg
				565					570					575	Ser
qeA	GTU	1111	٧dl	ser	ser	GIN	urg	ттр	1111	neu	וומח	⊐¢u	Ser	OT Å	Ω <del>C</del> T

```
585
Arg Tyr Phe Ile Glu Gln Pro Pro Leu Thr Ser Tyr Asp Glu Leu Asp
                          600
Arg Arg Met Arg Ala Gly Asp Ile Thr Val Ala Ile Glu Ile Pro Pro
                      615
                                         620
Asn Phe Gly Arg Asp Ile Ala Arg Gly Thr Pro Val Glu Leu Gly Val
                  630
                                     635
Trp Ile Asp Gly Ala Met Pro Ser Arg Ala Glu Thr Val Lys Gly Tyr
                                 650
Val Gln Ala Met His Gln Ser Trp Leu Gln Asp Val Ala Ser Arg Gln
                             665
Ser Thr Pro Ala Ser Gln Ser Gly Leu Met Asn Ile Glu Thr Arg Tyr
                       680
Arg Tyr Asn Pro Asp Val Lys Ser Leu Pro Ala Ile Val Pro Ala Val
                    695
                                        700
Ile Pro Leu Leu Met Met Ile Pro Ser Met Leu Ser Ala Leu Ser
               710
                                     715
Val Val Arg Glu Lys Glu Leu Gly Ser Ile Ile Asn Leu Tyr Val Thr
              725
                              730
Pro Thr Thr Arg Ser Glu Phe Leu Leu Gly Lys Gln Leu Pro Tyr Ile
                          745
          740
Ala Leu Gly Met Leu Asn Phe Phe Leu Leu Cys Gly Leu Ser Val Phe
                760
Val Phe Gly Val Pro His Lys Gly Ser Phe Leu Thr Leu Thr Leu Ala
                      775
Ala Leu Leu Tyr Ile Ile Ile Ala Thr Gly Met Gly Leu Leu Ile Ser
                                     795
Thr Phe Met Lys Ser Gln Ile Ala Ala Ile Phe Gly Thr Ala Ile Ile
             805
                                 810
Thr Leu Ile Pro Ala Thr Gln Phe Ser Gly Met Ile Asp Pro Val Ala
                   . 825
Ser Leu Glu Gly Pro Gly Arg Trp Ile Gly Glu Val Tyr Pro Thr Ser
                         840
                                    845
His Phe Leu Thr Ile Ala Arg Gly Thr Phe Ser Lys Ala Leu Asp Leu
                     855
                                        860
Thr Asp Leu Trp Gln Leu Phe Ile Pro Leu Leu Ile Ala Ile Pro Leu
               870
                                     875
Val Met Gly Leu Ser Ile Leu Leu Leu Lys Lys Gln Glu Gly
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<210> 435

<211> 355

<212> PRT

<213> Escherichia coli

## <400> 435

 Met
 Asp
 Lys
 Ser
 Lys
 Arg
 His
 Leu
 Ala
 Trp
 Trp
 Val
 Val
 Gly
 Leu
 Leu
 Leu
 Arg
 Pro
 Ala
 Gly
 Val
 Ala
 Gly
 Val
 Ala
 Gly
 Val
 Ala
 Gly
 Val
 Ala
 Gly
 Ala
 Ala
 Gly
 Arg
 Ile
 Ala
 Ile
 Ala
 Gly
 Arg
 Ile
 Ala
 Ala
 Gly
 Arg
 Ile
 Ala
 Ala
 Ile
 Ile
 Ala
 Ile
 Ala
 Ile
 Ala
 Ile
 Ile</th

```
Ser Glu Thr Arg Ala Ala Gln Ser Leu Val Asn Gln Arg Gln Ala Glu
            · 120
Leu Asp Ser Val Ala Lys Arg His Thr Arg Ser Arg Ser Leu Ala Gln
                      135
Arg Gly Ala Ile Ser Ala Gln Gln Leu Asp Asp Asp Arg Ala Ala Ala
                  150
                                      155
Glu Ser Ala Arg Ala Ala Leu Glu Ser Ala Lys Ala Gln Val Ser Ala
                                  170
Ser Lys Ala Ala Ile Glu Ala Ala Arg Thr Asn Ile Ile Gln Ala Gln
                              185
Thr Arg Val Glu Ala Ala Gln Ala Thr Glu Arg Arg Ile Ala Ala Asp
                         200
Ile Asp Asp Ser Glu Leu Lys Ala Pro Arg Asp Gly Arg Val Gln Tyr
                     215
                                         220
Arg Val Ala Glu Pro Gly Glu Val Leu Ala Ala Gly Gly Arg Val Leu
                  230
                                      235
Asn Met Val Asp Leu Ser Asp Val Tyr Met Thr Phe Phe Leu Pro Thr
                                 250
               245
Glu Gln Ala Gly Thr Leu Lys Leu Gly Gly Glu Ala Arg Leu Ile Leu
          260 265
Asp Ala Ala Pro Asp Leu Arg Ile Pro Ala Thr Ile Ser Phe Val Ala
                         280
Ser Val Ala Gln Phe Thr Pro Lys Thr Val Glu Thr Ser Asp Glu Arg
                      295
                                         300
Leu Lys Leu Met Phe Arg Val Lys Ala Arg Ile Pro Pro Glu Leu Leu
                                     315
                  310
Gln Gln His Leu Glu Tyr Val Lys Thr Gly Leu Pro Gly Val Ala Trp
                                 330
            325
Val Arg Val Asn Glu Glu Leu Pro Trp Pro Asp Asp Leu Val Val Arg
Leu Pro Gln
       355
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<212> PRT

<213> Escherichia coli

<400> 436

Met Tyr Arg Tyr Leu Ser Ile Ala Ala Val Val Leu Ser Ala Ala Phe 10 Ser Gly Pro Ala Leu Ala Glu Gly Ile Asn Ser Phe Ser Gln Ala Lys 25 Ala Ala Ala Val Lys Val His Ala Asp Ala Pro Gly Thr Phe Tyr Cys 40 Gly Cys Lys Ile Asn Trp Gln Gly Lys Lys Gly Val Val Asp Leu Gln 55 Ser Cys Gly Tyr Gln Val Arg Lys Asn Glu Asn Arg Ala Ser Arg Val ·· 75 70 Glu Trp Glu His Val Val Pro Ala Trp Gln Phe Gly His Gln Arg Gln 90 95 Cys Trp Gln Asp Gly Gly Arg Lys Asn Cys Ala Lys Asp Pro Val Tyr 105 110 Arg Lys Met Glu Ser Asp Met His Asn Leu Gln Pro Ser Val Gly Glu 120 115 Val Asn Gly Asp Arg Gly Asn Phe Met Tyr Ser Gln Trp Asn Gly Gly 135 140 Glu Gly Gln Tyr Gly Gln Cys Ala Met Lys Val Asp Phe Lys Glu Lys 155 ' . 150 Ala Ala Glu Pro Pro Ala Arg Ala Arg Gly Ala Ile Ala Arg Thr Tyr

165 170 Phe Tyr Met Arg Asp Gln Tyr Asn Leu Thr Leu Ser Arg Gln Gln Thr 180 185 Gln Leu Phe Asn Ala Trp Asn Lys Met Tyr Pro Val Thr Asp Trp Glu 200 205 Cys Glu Arg Asp Glu Arg Ile Ala Lys Val Gln Gly Asn His Asn Pro 215 Tyr Val Gln Arg Ala Cys Gln Ala Arg Lys Ser 230 <210> 437 <211> 480 <212> PRT <213> Escherichia coli Met Ser Arg Arg Leu Arg Arg Thr Lys Ile Val Thr Thr Leu Gly Pro 10 Ala Thr Asp Arg Asp Asn Asn Leu Glu Lys Val Ile Ala Ala Gly Ala 25 Asn Val Val Arg Met Asn Phe Ser His Gly Ser Pro Glu Asp His Lys Met Arg Ala Asp Lys Val Arg Glu Ile Ala Ala Lys Leu Gly Arg His 55 Val Ala Ile Leu Gly Asp Leu Gln Gly Pro Lys Ile Arg Val Ser Thr 70 75 Phe Lys Glu Gly Lys Val Phe Leu Asn Ile Gly Asp Lys Phe Leu Leu 85 90 Asp Ala Asn Leu Gly Lys Gly Glu Gly Asp Lys Glu Lys Val Gly Ile 105 Asp Tyr Lys Gly Leu Pro Ala Asp Val Val Pro Gly Asp Ile Leu Leu 120 Leu Asp Asp Gly Arg Val Gln Leu Lys Val Leu Glu Val Gln Gly Met 135 140 Lys Val Phe Thr Glu Val Thr Val Gly Gly Pro Leu Ser Asn Asn Lys 150 155 Gly Ile Asn Lys Leu Gly Gly Gly Leu Ser Ala Glu Ala Leu Thr Glu 170 165 Lys Asp Lys Ala Asp Ile Lys Thr Ala Ala Leu Ile Gly Val Asp Tyr 185 Leu Ala Val Ser Phe Pro Arg Cys Gly Glu Asp Leu Asn Tyr Ala Arg 200 Arg Leu Ala Arg Asp Ala Gly Cys Asp Ala Lys Ile Val Ala Lys Val 215 220 Glu Arg Ala Glu Ala Val Cys Ser Gln Asp Ala Met Asp Asp Ile Ile 230 Leu Ala Ser Asp Val Val Met Val Ala Arg Gly Asp Leu Gly Val Glu 245 250 Ile Gly Asp Pro Glu Leu Val Gly Ile Gln Lys Ala Leu Ile Arg Arg 265 Ala Arq Gln Leu Asn Arg Ala Val Ile Thr Ala Thr Gln Met Met Glu 280 Ser Met Ile Thr Asn Pro Met Pro Thr Arg Ala Glu Val Met Asp Val 295 300 Ala Asn Ala Val Leu Asp Gly Thr Asp Ala Val Met Leu Ser Ala Glu 310 Thr Ala Ala Gly Gln Tyr Pro Ser Glu Thr Val Ala Ala Met Ala Arg 325 330 Val Cys Leu Gly Ala Glu Lys Ile Pro Ser Ile Asn Val Ser Lys His 340 345 350

```
Arg Leu Asp Val Gln Phe Asp Asn Val Glu Glu Ala Ile Ala Met Ser
             360
Ala Met Tyr Ala Ala Asn His Leu Lys Gly Val Thr Ala Ile Ile Thr
                                    380
                   375
Met Thr Glu Ser Gly Arg Thr Ala Leu Met Thr Ser Arg Ile Ser Ser
                                395
               390
Gly Leu Pro Ile Phe Ala Met Ser Arg His Glu Arg Thr Leu Asn Leu
                             410
            405
Thr Ala Leu Tyr Arg Gly Val Thr Pro Val His Phe Asp Ser Ala Asn
                       425
         420
Asp Gly Val Ala Ala Ala Ser Glu Ala Val Asn Leu Leu Arg Asp Lys
           440
     435
Gly Tyr Leu Met Ser Gly Asp Leu Val Ile Val Thr Gln Gly Asp Val
 450 455 · 460
Met Ser Thr Val Gly Ser Thr Asn Thr Thr Arg Ile Leu Thr Val Glu
465 470
<210> 438
<211> 239
<212> PRT
<213> Escherichia coli
<400> 438
Met Ile Asn Val Leu Ile Ile Asp Asp Asp Ala Met Val Ala Glu Leu
                    10
Asn Arg Arg Tyr Val Ala Gln Ile Pro Gly Phe Gln Cys Cys Gly Thr
                          25
Ala Ser Thr Leu Glu Lys Ala Lys Glu Ile Ile Phe Asn Ser Asp Thr
                    40
Pro Ile Asp Leu Ile Leu Leu Asp Ile Tyr Met Gln Lys Glu Asn Gly
                55
Leu Asp Leu Leu Pro Val Leu His Asn Ala Arg Cys Lys Ser Asp Val
.65 70 75
Ile Val Ile Ser Ser Ala Ala Asp Ala Ala Thr Ile Lys Asp Ser Leu
                             90
             85
His Tyr Gly Val Val Asp Tyr Leu Ile Lys Pro Phe Gln Ala Ser Arg
        100 105
Phe Glu Glu Ala Leu Thr Gly Trp Arg Gln Lys Lys Met Ala Leu Glu
                                       125
      115 120
Lys His Gln Tyr Tyr Asp Gln Ala Glu Leu Asp Gln Leu Ile His Gly
                   135 . 140
Ser Ser Ser Asn Glu Gln Asp Pro Arg Arg Leu Pro Lys Gly Leu Thr
                                 155
      150
Pro Gln Thr Leu Arg Thr Leu Cys Gln Trp Ile Asp Ala His Gln Asp
    165 170
Tyr Glu Phe Ser Thr Asp Glu Leu Ala Asn Glu Val Asn Ile Ser Arg
   180
                          185
                                           190 .
Val Ser Cys Arg Lys Tyr Leu Ile Trp Leu Val Asn Cys His Ile Leu
 195 . 200
Phe Thr Ser Ile His Tyr Gly Val Thr Gly Arg Pro Val Tyr Arg Tyr
 210 215
Arg Ile Gln Ala Glu His Tyr Ser Leu Leu Lys Gln Tyr Cys Gln
                                235 .
                 230
<210> 439
<211> 543
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<212> PRT

<213> Escherichia coli

<400> 439 Met Arg His Ser Leu Pro Tyr Arg Met Leu Arg Lys Arg Pro Met Lys Leu Ser Thr Thr Val Ile Leu Met Val Ser Ala Val Leu Phe Ser Val Leu Leu Val Val His Leu Ile Tyr Phe Ser Gln Ile Ser Asp Met Thr 40 Arg Asp Gly Leu Ala Asn Lys Ala Leu Ala Val Ala Arg Thr Leu Ala 55 Asp Ser Pro Glu Ile Arg Gln Gly Leu Gln Lys Lys Pro Gln Glu Ser 70 Gly Ile Gln Ala Ile Ala Glu Ala Val Arg Lys Arg Asn Asp Leu Leu 85 90 Phe Ile Val Val Thr Asp Met Gln Ser Leu Arg Tyr Ser His Pro Glu 100 105 110 Ala Gln Arg Ile Gly Gln Pro Phe Lys Gly Asp Asp Ile Leu Lys Ala 125 120 Leu Asn Gly Glu Glu Asn Val Ala Ile Asn Arg Gly Phe Leu Ala Gln 135 140 Ala Leu Arg Val Phe Thr Pro Ile Tyr Asp Glu Asn His Lys Gln Ile 155 150 Gly Val Val Ala Ile Gly Leu Glu Leu Ser Arg Val Thr Gln Gln Ile 165 170 Asn Asp Ser Arg Trp Ser Ile Ile Trp Ser Val Leu Phe Gly Met Leu 185 Val Gly Leu Ile Gly Thr Cys Ile Leu Val Lys Val Leu Lys Lys Ile 200 Leu Phe Gly Leu Glu Pro Tyr Glu Ile Ser Thr Leu Phe Glu Gln Arg 215 Gln Ala Met Leu Gln Ser Ile Lys Glu Gly Val Val Ala Val Asp Asp 235 230 Arg Gly Glu Val Thr Leu Ile Asn Asp Ala Ala Gln Glu Leu Leu Asn 250 Tyr Arq Lys Ser Gln Asp Asp Glu Lys Leu Ser Thr Leu Ser His Ser 265 Trp Ser Gln Val Val Asp Val Ser Glu Val Leu Arg Asp Gly Thr Pro 280 285 Arg Arg Asp Glu Glu Ile Thr Ile Lys Asp Arg Leu Leu Leu Ile Asn 295 300 Thr Val Pro Val Arg Ser Asn Gly Val Ile Ile Gly Ala Ile Ser Thr 310 315 Phe Arg Asp Lys Thr Glu Val Arg Lys Leu Met Gln Arg Leu Asp Gly 325 330 Leu Val Asn Tyr Ala Asp Ala Leu Arg Glu Arg Ser His Glu Phe Met 345 340 Asn Lys Leu His Val Ile Leu Gly Leu Leu His Leu Lys Ser Tyr Lys 360 Gln Leu Glu Asp Tyr Ile Leu Lys Thr Ala Asn Asn Tyr Gln Glu Glu 375 Ile Gly Ser Leu Leu Gly Lys Ile Lys Ser Pro Val Ile Ala Gly Phe 390 395 Leu Ile Ser Lys Ile Asn Arg Ala Thr Asp Leu Gly His Thr Leu Ile 410 Leu Asn Ser Glu Ser Gln Leu Pro Asp Ser Gly Ser Glu Asp Gln Val 430 425 Ala Thr Leu Ile Thr Thr Leu Gly Asn Leu Ile Glu Asn Ala Leu Glu 440 Ala Leu Gly Pro Glu Pro Gly Gly Glu Ile Ser Val Thr Leu His Tyr 455 460 Arg His Gly Trp Leu His Cys Glu Val Asn Asp Asp Gly Pro Gly Ile

<210> 440 <211> 328 <212> PRT <213> Escherichia coli

Arg Ile Gly Ala Met Ala Arg Pro Phe Leu Lys Arg Arg Glu Ser Ile
65 70 75 80
Ala Arg Lys Asn Leu Glu Leu Cys Phe Pro Gln His Ser Ala Glu Glu

Arg Glu Lys Met Ile Ala Glu Asn Phe Arg Ser Leu Gly Met Ala Leu
100 :105 110

Val Glu Thr Gly Met Ala Trp Phe Trp Pro Asp Ser Arg Val Arg Lys
115 120 125

Trp Phe Asp Val Glu Gly Leu Asp Asn Leu Lys Arg Ala Gln Met Gln
130 135 140

Asn Arg Gly Val Met Val Val Gly Val His Phe Met Ser Leu Glu Leu
145 150 155 160

Gly Gly Arg Val Met Gly Leu Cys Gln Pro Met Met Ala Thr Tyr Arg 165 170 175 Pro His Asn Asn Gln Leu Met Glu Trp Val Gln Thr Arg Gly Arg Met

180 185 190
Arg Ser Asn Lys Ala Met Ile Gly Arg Asn Asn Leu Arg Gly Ile Val

Arg Ser Asn Lys Ala Met Ile Gly Arg Asn Asn Leu Arg Gly Ile Val

Gly Ala Leu Lys Lys Gly Glu Ala Val Trp Phe Ala Pro Asp Gln Asp 210 215 220

Tyr Gly Arg Lys Gly Ser Ser Phe Ala Pro Phe Phe Ala Val Glu Asn 225 230 235 240

Val Ala Thr Thr Asn Gly Thr Tyr Val Leu Ser Arg Leu Ser Gly Ala 245 250 255 Ala Met Leu Thr Val Thr Met Val Arg Lys Ala Asp Tyr Ser Gly Tyr

260 265 270

Arg Leu Phe Ile Thr Pro Glu Met Glu Gly Tyr Pro Thr Asp Glu Asn
275 280 285

275 280 285
Gln Ala Ala Ala Tyr Met Asn Lys Ile Ile Glu Lys Glu Ile Met Arg
290 295 300

Ala Pro Glu Gln Tyr Leu Trp Ile His Arg Arg Phe Lys Thr Arg Pro 305 310 315 320

Val Gly Glu Ser Ser Leu Tyr Ile 325

<210> 441

<211> 87 <212> PRT <213> Escherichia coli

<400> 441

 Met Ala Asn Ile Lys Ser Ala Lys Lys Arg Ala Ile Gln Ser Glu Lys 1
 5
 10
 15
 15

 Ala Arg Lys His Asn Ala Ser Arg Arg Ser Met Met Arg Thr Phe Ile 20
 25
 80
 15
 16
 15

 Lys Lys Lys Val Tyr Ala Ala Ala Ile Glu Ala Gly Asp Lys Ala Ala Ala Ala Gln 35
 40
 45
 45

 Lys Ala Phe Asn Glu Met Gln Pro Ile Val Asp 50
 60
 60
 60

 Gly Leu Ile His Lys Asn Lys Ala Ala Ala Arg His Lys Ala Asn Leu Thr 70
 75
 80

 Ala Gln Ile Asn Lys Leu Ala
 85

<210> 442 <211> 430 <212> PRT <213> Escherichia coli

<400> 442

Met Arg Tyr Asn Gly Leu Asn Asn Met Phe Phe Pro Leu Cys Leu Ile Asn Asp Asn His Ser Val Thr Ser Pro Ser His Thr Lys Lys Thr Lys Ser Asp Asn Tyr Ser Lys His His Lys Asn Thr Leu Ile Asp Asn Lys Ala Leu Ser Leu Phe Lys Met Asp Asp His Glu Lys Val Ile Gly Leu 55 60 Ile Gln Lys Met Lys Arg Ile Tyr Asp Ser Leu Pro Ser Gly Lys Ile 70 75 Thr Lys Glu Thr Asp Arg Lys Ile His Lys Tyr Phe Ile Asp Ile Ala 90 Ser His Ala Asn Asn Lys Cys Asp Asp Arg Ile Thr Arg Arg Val Tyr 105 Leu Asn Lys Asp Lys Glu Val Ser Ile Lys Val Val Tyr Phe Ile Asn 120 125 Asn Val Thr Val His Asn Asn Thr Ile Glu Ile Pro Gln Thr Val Asn 140 135 Gly Gly Tyr Asp Phe Ser His Leu Ser Leu Lys Gly Ile Val Ile Lys 155 150 Asp Glu Asp Leu Ser Asn Ser Asn Phe Ala Gly Cys Arg Leu Gln Asn 165 170 Ala Ile Phe Gln Asp Cys Asn Met Tyr Lys Thr Asn Phe Asn Phe Ala 185 Ile Met Glu Lys Ile Leu Phe Asp Asn Cys Ile Leu Asp Asp Ser Asn 200 Phe Ala Gln Ile Lys Met Thr Asp Gly Thr Leu Asn Ser Cys Ser Ala 215 Met His Val Gln Phe Tyr Asn Ala Thr Met Asn Arg Ala Asn Ile Lys 230 235 Asn Thr Phe Leu Asp Tyr Ser Asn Phe Tyr Met Ala Tyr Met Ala Glu 245 250 Val Asn Leu Tyr Lys Val Ile Ala Pro Tyr Ile Asn Leu Phe Arg Ala 265 260 Asp Leu Ser Phe Ser Lys Leu Asp Leu Ile Asn Phe Glu His Ala Asp 280

```
Leu Ser Arg Val Asn Leu Asn Lys Ala Thr Leu Gln Asn Ile Asn Leu
              295
Ile Asp Ser Lys Leu Phe Phe Thr Arg Leu Thr Asn Thr Phe Leu Glu
                                  315
             310
Met Val Ile Cys Thr Asp Ser Asn Met Ala Asn Val Asn Phe Asn Asn
                              330
             325
Ala Asn Leu Ser Asn Cys His Phe Asn Cys Ser Val Leu Thr Lys Ala
         340
                          345
Trp Met Phe Asn Ile Arg Leu Tyr Arg Val Asn Phe Asp Glu Ala Ser
 355 . 360
Val Gln Gly Met Gly Ile Thr Ile Leu Arg Gly Glu Glu Asn Ile Ser
                 375
Ile Asn Ser Asp Ile Leu Val Thr Leu Gln Lys Phe Phe Glu Glu Asp
                                 395 - 400
             390
Cys Ala Thr His Thr Gly Met Ser Gln Thr Glu Asp Asn Leu His Ala
                              410
           405
Val Ala Met Lys Ile Thr Ala Asp Ile Met Gln Asp Ala Asp
          420
                            425
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<210> 443 <211> 883 <212> PRT

<213> Escherichia coli

<400> 443 Met Asn Glu Gln Tyr Ser Ala Leu Arg Ser Asn Val Ser Met Leu Gly 10 Lys Val Leu Gly Glu Thr Ile Lys Asp Ala Leu Gly Glu His Ile Leu 25 Glu Arg Val Glu Thr Ile Arg Lys Leu Ser Lys Ser Ser Arg Ala Gly 40 Asn Asp Ala Asn Arg Gln Glu Leu Leu Thr Thr Leu Gln Asn Leu Ser 55 60 Asn Asp Glu Leu Leu Pro Val Ala Arg Ala Phe Ser Gln Phe Leu Asn 75 70 Leu Ala Asn Thr Ala Glu Gln Tyr His Ser Ile Ser Pro Lys Gly Glu 90 95 Ala Ala Ser Asn Pro Glu Val Ile Ala Arg Thr Leu Arg Lys Leu Lys 110 105 Asn Gln Pro Glu Leu Ser Glu Asp Thr Ile Lys Lys Ala Val Glu Ser 125 . 120 Leu Ser Leu Glu Leu Val Leu Thr Ala His Pro Thr Glu Ile Thr Arg 140 135 Arg Thr Leu Ile His Lys Met Val Glu Val Asn Ala Cys Leu Lys Gln 145 150 155 160 Leu Asp Asn Lys Asp Ile Ala Asp Tyr Glu His Asn Gln Leu Met Arg 170 165 Arg Leu Arg Gln Leu Ile Ala Gln Ser Trp His Thr Asp Glu Ile Arg 180 185 190 Lys Leu Arg Pro Ser Pro Val Asp Glu Ala Lys Trp Gly Phe Ala Val 200 205 Val Glu Asn Ser Leu Trp Gln Gly Val Pro Asn Tyr Leu Arg Glu Leu 215 220 Asn Glu Gln Leu Glu Glu Asn Leu Gly Tyr Lys Leu Pro Val Glu Phe 230 · 235 Val Pro Val Arg Phe Thr Ser Trp Met Gly Gly Asp Arg Asp Gly Asn 255 245 250 Pro Asn Val Thr Ala Asp Ile Thr Arg His Val Leu Leu Ser Arg 265 Trp Lys Ala Thr Asp Leu Phe Leu Lys Asp Ile Gln Val Leu Val Ser

		275					280					285			
Glu	Leu 290		Met	Val	Glu	Ala 295		Pro	Glu	Leu	Leu 300		Leu	Val	Gly
Glu 305	Glu	Gly	Ala	Ala	Glu 310	Pro	Tyr	Arg	Tyr	Leu 315	Met	Lys	Asn	Leu	Arg 320
Ser	Arg	Leu	Met	Ala 325	Thr	Gln	Ala	Trp	Leu 330	Glu	Ala	Arg	Leu	Lys 335	Gly
Glu	Glu	Leu	Pro 340	Lys	Pro	Glu	Gly	Leu 345	Leu	Thr	Gln	Asn	Glu 350	Glu	Leu
		355	Leu			Ā	360					365	_		
	370		Ala			375					380				
385			Val		390					395					400
_			Glu	405		_			410	_	_		_	415	_
_	-		Ser 420					425	_				430		
		435	Ser				440					445			
	450		Arg			455					460				
465		_	Ser		470		_			475			_		480
	_		Leu Pro	485					490				_	495	-
			500 Asp					505					510		
		515	Gln				520					525	_		
_	530		Ala			535					540			_	
545	_		Leu	_	550					555			_		560
			Gly	565	_				570		_			575	
			580 Leu					585					590		
		595	Glu				600					605	_	_	
	610		Val			615					620				
625					630				_	635	_				640
	•		Leu	645					650					655	
	_		Leu 660				•	665			_		670	_	
_		675	Lys	_			680	_		_		685			
	690		Gly	_		695					700		_	_	_
705			Gly		710			_		715		Ī			720
_			Asn	725					730			_		735	
			Lys 740					745					750		
met	cys	755	Asp	тrр	rro	rne	760	ser	TNT	wrd	теп	765	Met	тел	GLU

Met Val Phe Ala Lys Ala Asp Leu Trp Leu Ala Glu Tyr Tyr Asp Gln 775 Arg Leu Val Asp Lys Ala Leu Trp Pro Leu Gly Lys Glu Leu Arg Asn 795 Leu Gln Glu Glu Asp Ile Lys Val Val Leu Ala Ile Ala Asn Asp Ser 810 His Leu Met Ala Asp Leu Pro Trp Ile Ala Glu Ser Ile Gln Leu Arg 825 Asn Ile Tyr Thr Asp Pro Leu Asn Val Leu Gln Ala Glu Leu Leu His 840 Arg Ser Arg Gln Ala Glu Lys Glu Gly Gln Glu Pro Asp Pro Arg Val 855 860 . Glu Gln Ala Leu Met Val Thr Ile Ala Gly Ile Ala Ala Gly Met Arg 875 Asn Thr Gly

<210> 444 <211> 663 <212> PRT <213> Escherichia coli

<400> 444

Met Ser Ser Arg Lys Glu Leu Ala Asn Ala Ile Arg Ala Leu Ser Met 10 Asp Ala Val Gln Lys Ala Lys Ser Gly His Pro Gly Ala Pro Met Gly 25 Met Ala Asp Ile Ala Glu Val Leu Trp Arg Asp Phe Leu Lys His Asn 40 Pro Gln Asn Pro Ser Trp Ala Asp Arg Asp Arg Phe Val Leu Ser Asn 55 60 Gly His Gly Ser Met Leu Ile Tyr Ser Leu Leu His Leu Thr Gly Tyr Asp Leu Pro Met Glu Glu Leu Lys Asn Phe Arg Gln Leu His Ser Lys Thr Pro Gly His Pro Glu Val Gly Tyr Thr Ala Gly Val Glu Thr Thr 105 Thr Gly Pro Leu Gly Gln Gly Ile Ala Asn Ala Val Gly Met Ala Ile 120 . 125 Ala Glu Lys Thr Leu Ala Ala Gln Phe Asn Arg Pro Gly His Asp Ile 135 · 140 Val Asp His Tyr Thr Tyr Ala Phe Met Gly Asp Gly Cys Met Met Glu 155 150 Gly Ile Ser His Glu Val Cys Ser Leu Ala Gly Thr Leu Lys Leu Gly 170 Lys Leu Ile Ala Phe Tyr Asp Asp Asn Gly Ile Ser Ile Asp Gly His 185 Val Glu Gly Trp Phe Thr Asp Asp Thr Ala Met Arg Phe Glu Ala Tyr 200 Gly Trp His Val Ile Arg Asp Ile Asp Gly His Asp Ala Ala Ser Ile 215 220 Lys Arg Ala Val Glu Glu Ala Arg Ala Val Thr Asp Lys Pro Ser Leu 230 235 Leu Met Cys Lys Thr Ile Ile Gly Phe Gly Ser Pro Asn Lys Ala Gly 245 250 Thr His Asp Ser His Gly Ala Pro Leu Gly Asp Ala Glu Ile Ala Leu 260 265 270 Thr Arg Glu Gln Leu Gly Trp Lys Tyr Ala Pro Phe Glu Ile Pro Ser 280 Glu Ile Tyr Ala Gln Trp Asp Ala Lys Glu Ala Gly Gln Ala Lys Glu

```
295
                                           300
Ser Ala Trp Asn Glu Lys Phe Ala Ala Tyr Ala Lys Ala Tyr Pro Gln
                                       315
                   310
Glu Ala Ala Glu Phe Thr Arg Arg Met Lys Gly Glu Met Pro Ser Asp
               325
                                   330
Phe Asp Ala Lys Ala Lys Glu Phe Ile Ala Lys Leu Gln Ala Asn Pro
                               345
Ala Lys Ile Ala Ser Arg Lys Ala Ser Gln Asn Ala Ile Glu Ala Phe
                           360
Gly Pro Leu Leu Pro Glu Phe Leu Gly Gly Ser Ala Asp Leu Ala Pro
                       375
                                           380
Ser Asn Leu Thr Leu Trp Ser Gly Ser Lys Ala Ile Asn Glu Asp Ala
                   390
                                      395
Ala Gly Asn Tyr Ile His Tyr Gly Val Arg Glu Phe Gly Met Thr Ala
               405
                                   410
Ile Ala Asn Gly Ile Ser Leu His Gly Gly Phe Leu Pro Tyr Thr Ser
                               425
Thr Phe Leu Met Phe Val Glu Tyr Ala Arg Asn Ala Val Arg Met Ala
                          440
Ala Leu Met Lys Gln Arg Gln Val Met Val Tyr Thr His Asp Ser Ile
                       455
                                          460
Gly Leu Gly Glu Asp Gly Pro Thr His Gln Pro Val Glu Gln Val Ala
                   470
                                       475
Ser Leu Arg Val Thr Pro Asn Met Ser Thr Trp Arg Pro Cys Asp Gln
                                   490
              485
Val Glu Ser Ala Val Ala Trp Lys Tyr Gly Val Glu Arg Gln Asp Gly
                              505
Pro Thr Ala Leu Ile Leu Ser Arg Gln Asn Leu Ala Gln Gln Glu Arg
                           520
Thr Glu Glu Gln Leu Ala Asn Ile Ala Arg Gly Gly Tyr Val Leu Lys
                       535
Asp Cys Ala Gly Gln Pro Glu Leu Ile Phe Ile Ala Thr Gly Ser Glu
                                       555
                  550
Val Glu Leu Ala Val Ala Ala Tyr Glu Lys Leu Thr Ala Glu Gly Val
               565
                                  570
Lys Ala Arg Val Val Ser Met Ser Ser Thr Asp Ala Phe Asp Lys Gln
                               585
Asp Ala Ala Tyr Arg Glu Ser Val Leu Pro Lys Ala Val Thr Ala Arg
                           600
Val Ala Val Glu Ala Gly Ile Ala Asp Tyr Trp Tyr Lys Tyr Val Gly
                       615
Leu Asn Gly Ala Ile Val Gly Met Thr Thr Phe Gly Glu Ser Ala Pro
                   630
                                       635
Ala Glu Leu Leu Phe Glu Glu Phe Gly Phe Thr Val Asp Asn Val Val
               645
                                   650
Ala Lys Ala Lys Glu Leu Leu
           660
```

<210> 445

<211> 152

<212> PRT

<213> Escherichia coli

## <400> 445

 Met Phe Arg Gly Ala Thr Leu Val Asn Leu Asp Ser Lys Gly Arg Leu

 1
 5
 10
 15

 Ser Val Pro Thr Arg Tyr Arg Glu Gln Leu Leu Glu Asn Ala Ala Gly
 20
 25
 30

 Gln Met Val Cys Thr Ile Asp Ile Tyr His Pro Cys Leu Leu Leu Tyr
 40
 45

 Pro
 Leu
 Pro
 Glu
 Trp
 Glu
 Ile
 Ile
 Glu
 Glu
 Glu
 Leu
 Glu
 Leu
 Ser
 Arg
 Leu
 Leu
 Leu
 Leu
 Leu
 Gly
 His
 Ala
 Gly
 Ala
 Gly
 Arg
 Glu
 Arg
 Leu
 Leu
 Leu
 Leu
 Leu
 Ile
 Ala
 Pro

 Val
 Leu
 Arg
 Glu
 His
 Ala
 Gly
 Leu
 Thr
 Lys
 Glu
 Val
 Met
 Leu
 Val
 Gly
 Leu
 Thr
 Lys
 Glu
 Val
 Met
 Leu
 Val
 Gly
 Gly
 Inc
 Inc

<210> 446 <211> 313 <212> PRT <213> Escherichia coli

Gly Arg Leu Leu Ala Ile Asp Arg Asp Pro Gln Ala Ile Ala Val Ala 50 55 60

Lys Thr Ile Asp Asp Pro Arg Phe Ser Ile Ile His Gly Pro Phe Ser 65 70 75 80

Ala Leu Gly Glu Tyr Val Ala Glu Arg Asp Leu Ile Gly Lys Ile Asp 85 90 95

Gly Ile Leu Leu Asp Leu Gly Val Ser Ser Pro Gln Leu Asp Asp Ala

100

Glu Arg Gly Phe Ser Phe Met Arg Asp Gly Pro Leu Asp Met Arg Met

115

120

125

Asp Pro Thr Arg Gly Gln Ser Ala Ala Glu Trp Leu Gln Thr Ala Glu 130 135 140 Glu Ala Asp Ile Ala Trp Val Leu Lys Thr Tyr Gly Glu Glu Arg Phe

145 150 155 160

Ala Lys Arg Ile Ala Arg Ala Ile Val Glu Arg Asn Arg Glu Gln Pro
165 170 175

Met Thr Arg Thr Lys Glu Leu Ala Glu Val Val Ala Ala Ala Thr Pro 180 185 190

Val Lys Asp Lys Phe Lys His Pro Ala Thr Arg Thr Phe Gln Ala Val 195 200 205

Arg Ile Trp Val Asn Ser Glu Leu Glu Glu Ile Glu Gln Ala Leu Lys 210 215 220

Ser Ser Leu Asn Val Leu Ala Pro Gly Gly Arg Leu Ser Ile Ile Ser 225 230 235 240

Phe His Ser Leu Glu Asp Arg Ile Val Lys Arg Phe Met Arg Glu Asn 245 250 255

Ser Arg Gly Pro Gln Val Pro Ala Gly Leu Pro Met Thr Glu Glu Gln 260 265 270

Leu Lys Lys Leu Gly Gly Arg Gln Leu Arg Ala Leu Gly Lys Leu Met 275 280 285

Pro Gly Glu Glu Val Ala Glu Asn Pro Arg Ala Arg Ser Ser Val 290 295 300

Leu Arg Ile Ala Glu Arg Thr Asn Ala

305 310

<210> 447

<211> 121

<212> PRT

<213> Escherichia coli

<400> 447

Ser Gln Glu Asn Ile Val Val Gln Lys 115 120

<210> 448

<211> 588

<212> PRT

<213> Escherichia coli

<400> 448

Met Lys Ala Ala Ala Lys Thr Gln Lys Pro Lys Arg Gln Glu Glu His 10 Ala Asn Phe Ile Ser Trp Arg Phe Ala Leu Leu Cys Gly Cys Ile Leu 25 Leu Ala Leu Ala Phe Leu Leu Gly Arg Val Ala Trp Leu Gln Val Ile 40 Ser Pro Asp Met Leu Val Lys Glu Gly Asp Met Arg Ser Leu Arg Val 55 Gln Gln Val Ser Thr Ser Arg Gly Met Ile Thr Asp Arg Ser Gly Arg 70 Pro Leu Ala Val Ser Val Pro Val Lys Ala Ile Trp Ala Asp Pro Lys Glu Val His Asp Ala Gly Gly Ile Ser Val Gly Asp Arg Trp Lys Ala 105 Leu Ala Asn Ala Leu Asn Ile Pro Leu Asp Gln Leu Ser Ala Arg Ile 120 Asn Ala Asn Pro Lys Gly Arg Phe Ile Tyr Leu Ala Arg Gln Val Asn 135 Pro Asp Met Ala Asp Tyr Ile Lys Lys Leu Lys Leu Pro Gly Ile His 150 155 Leu Arg Glu Glu Ser Arg Arg Tyr Tyr Pro Ser Gly Glu Val Thr Ala 170 165 His Leu Ile Gly Phe Thr Asn Val Asp Ser Gln Gly Ile Glu Gly Val 185 Glu Lys Ser Phe Asp Lys Trp Leu Thr Gly Gln Pro Gly Glu Arg Ile 200 Val Arg Lys Asp Arg Tyr Gly Arg Val Ile Glu Asp Ile Ser Ser Thr 215

```
Asp Ser Gln Ala Ala His Asn Leu Ala Leu Ser Ile Asp Glu Arg Leu
              230
                          235
Gln Ala Leu Val Tyr Arg Glu Leu Asn Asn Ala Val Ala Phe Asn Lys
              245
                                 250
Ala Glu Ser Gly Ser Ala Val Leu Val Asp Val Asn Thr Gly Glu Val
         260
                             265
Leu Ala Met Ala Asn Ser Pro Ser Tyr Asn Pro Asn Asn Leu Ser Gly
                          280
Thr Pro Lys Glu Ala Met Arg Asn Arg Thr Ile Thr Asp Val Phe Glu
                  295
                                        300
Pro Gly Ser Thr Val Lys Pro Met Val Val Met Thr Ala Leu Gln Arg
                                     315
                  310
Gly Val Val Arg Glu Asn Ser Val Leu Asn Thr Ile Pro Tyr Arg Ile
              325
                                 330
Asn Gly His Glu Ile Lys Asp Val Ala Arg Tyr Ser Glu Leu Thr Leu
                             345
          340
Thr Gly Val Leu Gln Lys Ser Ser Asn Val Gly Val Ser Lys Leu Ala
                         360
       355
Leu Ala Met Pro Ser Ser Ala Leu Val Asp Thr Tyr Ser Arg Phe Gly
 370 : 375
                                        380 .
Leu Gly Lys Ala Thr Asn Leu Gly Leu Val Gly Glu Arg Ser Gly Leu
                                    395
                  390
Tyr Pro Gln Lys Gln Arg Trp Ser Asp Ile Glu Arg Ala Thr Phe Ser
              405
                                 410
Phe Gly Tyr Gly Leu Met Val Thr Pro Leu Gln Leu Ala Arg Val Tyr
          420
                             425
Ala Thr Ile Gly Ser Tyr Gly Ile Tyr Arg Pro Leu Ser Ile Thr Lys
                         440
                                            445
Val Asp Pro Pro Val Pro Gly Glu Arg Val Phe Pro Glu Ser Ile Val
                     455
Arg Thr Val Val His Met Met Glu Ser Val Ala Leu Pro Gly Gly Gly
                  470
                                    475
Gly Val Lys Ala Ala Ile Lys Gly Tyr Arg Ile Ala Ile Lys Thr Gly
                                 490
Thr Ala Lys Lys Val Gly Pro Asp Gly Arg Tyr Ile Asn Lys Tyr Ile
                            505
Ala Tyr Thr Ala Gly Val Ala Pro Ala Ser Gln Pro Arg Phe Ala Leu
                         520 . 525
Val Val Val Ile Asn Asp Pro Gln Ala Gly Lys Tyr Tyr Gly Gly Ala
                    535 . 540
Val Ser Ala Pro Val Phe Gly Ala Ile Met Gly Gly Val Leu Arg Thr
                                 555
                  550 '
Met Asn Ile Glu Pro Asp Ala Leu Thr Thr Gly Asp Lys Asn Glu Phe
              565 ·
                               570
Val Ile Asn Gln Gly Glu Gly Thr Gly Gly Arg Ser
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<210> 449

<211> 495

<212> PRT

<213> Escherichia coli

<400> 449

 Met Ala Asp Arg Asp Arg Asp Leu Arg Asp Leu Leu Ala Pro Trp Val Pro Asp

 1
 5
 10
 15

 Ala Pro Ser Arg Ala Leu Arg Glu Met Thr Leu Asp Ser Arg Val Ala
 20
 25
 30

 Ala Ala Gly Asp Leu Phe Val Ala Val Val Gly His Gln Ala Asp Gly
 35
 40
 45

 Arg Arg Tyr Ile Pro Gln Ala Ile Ala Gln Gly Val Ala Ala Ile Ile

```
Ala Glu Ala Lys Asp Glu Ala Thr Asp Gly Glu Ile Arg Glu Met His
Gly Val Pro Val Ile Tyr Leu Ser Gln Leu Asn Glu Arg Leu Ser Ala
                                   90
Leu Ala Gly Arg Phe Tyr His Glu Pro Ser Asp Asn Leu Arg Leu Val
                              105
Gly Val Thr Gly Thr Asn Gly Lys Thr Thr Thr Thr Gln Leu Leu Ala
       115
                           120
                                              125
Gln Trp Ser Gln Leu Leu Gly Glu Ile Ser Ala Val Met Gly Thr Val
                       135
Gly Asn Gly Leu Leu Gly Lys Val Ile Pro Thr Glu Asn Thr Thr Gly
                  150
                                     155
Ser Ala Val Asp Val Gln His Glu Leu Ala Gly Leu Val Asp Gln Gly
              165
                                  170
Ala Thr Phe Cys Ala Met Glu Val Ser Ser His Gly Leu Val Gln His
                              185
           180
Arg Val Ala Ala Leu Lys Phe Ala Ala Ser Val Phe Thr Asn Leu Ser
       195
                          200
Arg Asp His Leu Asp Tyr His Gly Asp Met Glu His Tyr Glu Ala Ala
                      215
                                          220
Lys Trp Leu Leu Tyr Ser Glu His His Cys Gly Gln Ala Ile Ile Asn
                  230
                                      235
Ala Asp Asp Glu Val Gly Arg Arg Trp Leu Ala Lys Leu Pro Asp Ala
              245
                                  250
Val Ala Val Ser Met Glu Asp His Ile Asn Pro Asn Cys His Gly Arg
                              265
Trp Leu Lys Ala Thr Glu Val Asn Tyr His Asp Ser Gly Ala Thr Ile
                          280
Arg Phe Ser Ser Trp Gly Asp Gly Glu Ile Glu Ser His Leu Met
                      295
                                          300
Gly Ala Phe Asn Val Ser Asn Leu Leu Leu Ala Leu Ala Thr Leu Leu
                  310
                                      315
Ala Leu Gly Tyr Pro Leu Ala Asp Leu Leu Lys Thr Ala Ala Arg Leu
                                  330
Gln Pro Val Cys Gly Arg Met Glu Val Phe Thr Ala Pro Gly Lys Pro
                               345
Thr Val Val Val Asp Tyr Ala His Thr Pro Asp Ala Leu Glu Lys Ala
                          360
                                              365
Leu Gln Ala Ala Arg Leu His Cys Ala Gly Lys Leu Trp Cys Val Phe
                                           380
                      375
Gly Cys Gly Gly Asp Arg Asp Lys Gly Lys Arg Pro Leu Met Gly Ala
                   390
                                      395
Ile Ala Glu Glu Phe Ala Asp Val Ala Val Val Thr Asp Asp Asn Pro
                                   410
               405
Arg Thr Glu Glu Pro Arg Ala Ile Ile Asn Asp Ile Leu Ala Gly Met
                               425
Leu Asp Ala Gly His Ala Lys Val Met Glu Gly Arg Ala Glu Ala Val
                           440
Thr Cys Ala Val Met Gln Ala Lys Glu Asn Asp Val Val Leu Val Ala
                       455
                                           460
Gly Lys Gly His Glu Asp Tyr Gln Ile Val Gly Asn Gln Arg Leu Asp
                                       475
                   470
Tyr Ser Asp Arg Val Thr Val Ala Arg Leu Leu Gly Val Ile Ala
```

<210> 450

<211> 452

<212> PRT

<213> Escherichia coli

<400> 450															
Met 1	Ile	Ser		5					10					Gly 15	
		_	20	_				25					30	Thr	
_		35					40					45		Arg	
_	50		_			55					60			Gly	
65					70					75					, 80
_	_		_	85					90					Arg 95	
			100	-				105					110	Lys	
		115	•				120					125		Asn	
	130					135					140			Met	
145					150					155				Leu	160
•				165					170			٠.		Arg 175	
			180					185					190	Gly	
_		195		-			200					205		Ser	
	210					215					220			Asp	
225		_			230					235				Phe	240
				245					250					Val 255	
			260					265					270	Val	
		275					280					285		Leu	
	290					295			•		300			Ile	
305	_				310					315				Pro	320
				325					330					Ala 335	
	_		340					345					350		Gly
_		355					360			•		365	•	Glu	
	370					375				•	380	• ;		Gly	
385	_				390					395					Ala 400
				405					410					415	
			420					425					430		Lys
		435		Ala	Ala	Met	Glu 440		Val	Val	Arg	Ala 445		Gln	Glu
Asn	Gly 450	Thr	СЛЗ												

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<210> 451
<211> 360
<212> PRT
<213> Escherichia coli
<400> 451
Met Leu Val Trp Leu Ala Glu His Leu Val Lys Tyr Tyr Ser Gly Phe
                                   10
Asn Val Phe Ser Tyr Leu Thr Phe Arg Ala Ile Val Ser Leu Leu Thr
                               25
Ala Leu Phe Ile Ser Leu Trp Met Gly Pro Arg Met Ile Ala His Leu
                           40
Gln Lys Leu Ser Phe Gly Gln Val Val Arg Asn Asp Gly Pro Glu Ser
                       55
His Phe Ser Lys Arg Gly Thr Pro Thr Met Gly Gly Ile Met Ile Leu
Thr Ala Ile Val Ile Ser Val Leu Leu Trp Ala Tyr Pro Ser Asn Pro
                                  90
Tyr Val Trp Cys Val Leu Val Val Leu Val Gly Tyr Gly Val Ile Gly
                              105
Phe Val Asp Asp Tyr Arg Lys Val Val Arg Lys Asp Thr Lys Gly Leu
                          120
Ile Ala Arg Trp Lys Tyr Phe Trp Met Ser Val Ile Ala Leu Gly Val
                      135
Ala Phe Ala Leu Tyr Leu Ala Gly Lys Asp Thr Pro Ala Thr Gln Leu
                  150
Val Val Pro Phe Phe Lys Asp Val Met Pro Gln Leu Gly Leu Phe Tyr
                                  170
Ile Leu Leu Ala Tyr Phe Val Ile Val Gly Thr Gly Asn Ala Val Asn
                              185
Leu Thr Asp Gly Leu Asp Gly Leu Ala Ile Met Pro Thr Val Phe Val
                          200
Ala Gly Gly Phe Ala Leu Val Ala Trp Ala Thr Gly Asn Met Asn Phe
                                          220
                      215
Ala Ser Tyr Leu His Ile Pro Tyr Leu Arg His Ala Gly Glu Leu Val
        230
                                      235
Ile Val Cys Thr Ala Ile Val Gly Ala Gly Leu Gly Phe Leu Trp Phe
           245
                                  250
Asn Thr Tyr Pro Ala Gln Val Phe Met Gly Asp Val Gly Ser Leu Ala
                              265
Leu Gly Gly Ala Leu Gly Ile Ile Ala Val Leu Leu Arg Gln Glu Phe
                          280
Leu Leu Val Ile Met Gly Gly Val Phe Val Val Glu Thr Leu Ser Val
                       295
                                          300
Ile Leu Gln Val Gly Ser Phe Lys Leu Arg Gly Gln Arg Ile Phe Arg
                   310
                                       315
Met Ala Pro Ile His His His Tyr Glu Leu Lys Gly Trp Pro Glu Pro
                                   330
Arg Val Ile Val Arg Phe Trp Ile Ile Ser Leu Met Leu Val Leu Ile
Gly Leu Ala Thr Leu Lys Val Arg
       355
                           360
<210> 452
<211> 438
<212> PRT
<213> Escherichia coli
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-460-

<400> 452

```
Met Ala Asp Tyr Gln Gly Lys Asn Val Val Ile Ile Gly Leu Gly Leu
                 . 10
Thr Gly Leu Ser Cys Val Asp Phe Phe Leu Ala Arg Gly Val Thr Pro
Arg Val Met Asp Thr Arg Met Thr Pro Pro Gly Leu Asp Lys Leu Pro
                      40
Glu Ala Val Glu Arq His Thr Gly Ser Leu Asn Asp Glu Trp Leu Met
Ala Ala Asp Leu Ile Val Ala Ser Pro Gly Ile Ala Leu Ala His Pro
65 70
Ser Leu Ser Ala Ala Ala Asp Ala Gly Ile Glu Ile Val Gly Asp Ile
       · 85
Glu Leu Phe Cys Arg Glu Ala Gln Ala Pro Ile Val Ala Ile Thr Gly
        100 · 105
Ser Asn Gly Lys Ser Thr Val Thr Thr Leu Val Gly Glu Met Ala Lys
                      120
Ala Ala Gly Val Asn Val Gly Val Gly Asn Ile Gly Leu Pro Ala
        135
Leu Met Leu Leu Asp Asp Glu Cys Glu Leu Tyr Val Leu Glu Leu Ser
               150 155
Ser Phe Gln Leu Glu Thr Thr Ser Ser Leu Gln Ala Val Ala Ala Thr
            165 170
Ile Leu Asn Val Thr Glu Asp His Met Asp Arg Tyr Pro Phe Gly Leu
                         185
Gln Gln Tyr Arg Ala Ala Lys Leu Arg Ile Tyr Glu Asn Ala Lys Val
 195 200
Cys Val Val Asn Ala Asp Asp Ala Leu Thr Met Pro Ile Arg Gly Ala
                  215
Asp Glu Arg Cys Val Ser Phe Gly Val Asn Met Gly Asp Tyr His Leu
                                235 · 240
               230
Asn His Gln Gln Gly Glu Thr Trp Leu Arg Val Lys Gly Glu Lys Val
            245 250
Leu Asn Val Lys Glu Met Lys Leu Ser Gly Gln His Asn Tyr Thr Asn
                   265
Ala Leu Ala Ala Leu Ala Leu Ala Asp Ala Ala Gly Leu Pro Arg Ala
               280
Ser Ser Leu Lys Ala Leu Thr Thr Phe Thr Gly Leu Pro His Arg Phe
                  295
Glu Val Val Leu Glu His Asn Gly Val Arg Trp Ile Asn Asp Ser Lys
                310 . 315
Ala Thr Asn Val Gly Ser Thr Glu Ala Ala Leu Asn Gly Leu His Val
                             330 335
Asp Gly Thr Leu His Leu Leu Leu Gly Gly Asp Gly Lys Ser Ala Asp
                345
Phe Ser Pro Leu Ala Arg Tyr Leu Asn Gly Asp Asn Val Arg Leu Tyr
                    360 . 365
Cys Phe Gly Arg Asp Gly Ala Gln Leu Ala Ala Leu Arg Pro Glu Val
                   375
                           380
Ala Glu Gln Thr Glu Thr Met Glu Gln Ala Met Arg Leu Leu Ala Pro
                                395 . 400
       390
Arg Val Gln Pro Gly Asp Met Val Leu Leu Ser Pro Ala Cys Ala Ser
                           410
                                              415
       405
Leu Asp Gln Phe Lys Asn Phe Glu Gln Arg Gly Asn Glu Phe Ala Arg
                          425
Leu Ala Lys Glu Leu Gly
      435
```

<210> 453

<211> 414

<212> PRT

## <213> Escherichia coli

<400> 453 Met Arg Leu Ser Leu Pro Arg Leu Lys Met Pro Arg Leu Pro Gly Phe Ser Ile Leu Val Trp Ile Ser Thr Ala Leu Lys Gly Trp Val Met Gly Ser Arg Glu Lys Asp Thr Asp Ser Leu Ile Met Tyr Asp Arg Thr Leu 40 Leu Trp Leu Thr Phe Gly Leu Ala Ala Ile Gly Phe Ile Met Val Thr Ser Ala Ser Met Pro Ile Gly Gln Arg Leu Thr Asn Asp Pro Phe Phe 70 75 Phe Ala Lys Arg Asp Gly Val Tyr Leu Ile Leu Ala Phe Ile Leu Ala 90 Ile Ile Thr Leu Arg Leu Pro Met Glu Phe Trp Gln Arg Tyr Ser Ala 100 105 110 Thr Met Leu Leu Gly Ser Ile Ile Leu Leu Met Ile Val Leu Val Val 120 Gly Ser Ser Val Lys Gly Ala Ser Arg Trp Ile Asp Leu Gly Leu Leu 135 Arg Ile Gln Pro Ala Glu Leu Thr Lys Leu Ser Leu Phe Cys Tyr Ile 150 155 Ala Asn Tyr Leu Val Arg Lys Gly Asp Glu Val Arg Asn Asn Leu Arg 165 170 Gly Phe Leu Lys Pro Met Gly Val Ile Leu Val Leu Ala Val Leu Leu 180 185 Leu Ala Gln Pro Asp Leu Gly Thr Val Val Val Leu Phe Val Thr Thr 200 Leu Ala Met Leu Phe Leu Ala Gly Ala Lys Leu Trp Gln Phe Ile Ala 215 Ile Ile Gly Met Gly Ile Ser Ala Val Val Leu Leu Ile Leu Ala Glu 235 230 Pro Tyr Arg Ile Arg Arg Val Thr Ala Phe Trp Asn Pro Trp Glu Asp 250 Pro Phe Gly Ser Gly Tyr Gln Leu Thr Gln Ser Leu Met Ala Phe Gly 265 Arg Gly Glu Leu Trp Gly Gln Gly Leu Gly Asn Ser Val Gln Lys Leu 280 Glu Tyr Leu Pro Glu Ala His Thr Asp Phe Ile Phe Ala Ile Ile Gly 295 Glu Glu Leu Gly Tyr Val Gly Val Val Leu Ala Leu Leu Met Val Phe 310 315 Phe Val Ala Phe Arg Ala Met Ser Ile Gly Arg Lys Ala Leu Glu Ile 330 Asp His Arg Phe Ser Gly Phe Leu Ala Cys Ser Ile Gly Ile Trp Phe 345 Ser Phe Gln Ala Leu Val Asn Val Gly Ala Ala Ala Gly Met Leu Pro 360 Thr Lys Gly Leu Thr Leu Pro Leu Ile Ser Tyr Gly Gly Ser Ser Leu 375 380 Leu Ile Met Ser Thr Ala Ile Met Met Leu Leu Arg Ile Asp Tyr Glu 390 395 Thr Arg Leu Glu Lys Ala Gln Ala Phe Val Arg Gly Ser Arg

<210> 454

<211> 355

<212> PRT

<213> Escherichia coli

```
<400> 454
Met Ser Gly Gln Gly Lys Arg Leu Met Val Met Ala Gly Gly Thr Gly
                                  10
Gly His Val Phe Pro Gly Leu Ala Val Ala His His Leu Met Ala Gln
                               25
Gly Trp Gln Val Arg Trp Leu Gly Thr Ala Asp Arg Met Glu Ala Asp
                          40
Leu Val Pro Lys His Gly Ile Glu Ile Asp Phe Ile Arg Ile Ser Gly
                       55
Leu Arg Gly Lys Gly Ile Lys Ala Leu Ile Ala Ala Pro Leu Arg Ile
                                      75
Phe Asn Ala Trp Arg Gln Ala Arg Ala Ile Met Lys Ala Tyr Lys Pro
Asp Val Val Leu Gly Met Gly Gly Tyr Val Ser Gly Pro Gly Gly Leu
                               105
Ala Ala Trp Ser Leu Gly Ile Pro Val Val Leu His Glu Gln Asn Gly
                           120
Ile Ala Gly Leu Thr Asn Lys Trp Leu Ala Lys Ile Ala Thr Lys Val
           135
Met Gln Ala Phe Pro Gly Ala Phe Pro Asn Ala Glu Val Val Gly Asn
                   150
                                      155
Pro Val Arg Thr Asp Val Leu Ala Leu Pro Leu Pro Gln Gln Arg Leu
                                  170
               165 .
Ala Gly Arg Glu Gly Pro Val Arg Val Leu Val Val Gly Gly Ser Gln
           180
                               185 .
Gly Ala Arg Ile Leu Asn Gln Thr Met Pro Gln Val Ala Ala Lys Leu
                           200
Gly Asp Ser Val Thr Ile Trp His Gln Ser Gly Lys Gly Ser Gln Gln
                       215
                                          220
Ser Val Glu Gln Ala Tyr Ala Glu Ala Gly Gln Pro Gln His Lys Val
                   230
                                      235
Thr Glu Phe Ile Asp Asp Met Ala Ala Ala Tyr Ala Trp Ala Asp Val
                                  250
Val Val Cys Arg Ser Gly Ala Leu Thr Val Ser Glu Ile Ala Ala Ala
           260
                               265
Gly Leu Pro Ala Leu Phe Val Pro Phe Gln His Lys Asp Arg Gln Gln
                           280
Tyr Trp Asn Ala Leu Pro Leu Glu Lys Ala Gly Ala Ala Lys Ile Ile
   290 . 295
                                          300
Glu Gln Pro Gln Leu Ser Val Asp Ala Val Ala Asn Thr Leu Ala Gly
                                      315
                   310
Trp Ser Arg Glu Thr Leu Leu Thr Met Ala Glu Arg Ala Arg Ala Ala
                                  330
               325
Ser Ile Pro Asp Ala Thr Glu Arg Val Ala Asn Glu Val Ser Arg Val
                               345
           340
                                                  350
Ala Arg Ala
       355
```

<210> 455

<211> 491

<212> PRT

<213> Escherichia coli

<400> 455

Met Asn Thr Gln Gln Leu Ala Lys Leu Arg Ser Ile Val Pro Glu Met

1 5 10 15

Arg Arg Val Arg His Ile His Phe Val Gly Ile Gly Gly Ala Gly Met
20 25 30

Gly Gly Ile Ala Glu Val Leu Ala Asn Glu Gly Tyr Gln Ile Ser Gly

		35					40					45			
Ser	Asp 50	Leu	Ala	Pro	Asn	Pro 55	Val	Thr	Gln	Gln	Leu 60	Met	Asn	Leu	Gly
65			-		70		_			75				Ala	80
Val	Val	Val	Val	Ser 85	Ser	Ala	Ile	Ser	Ala 90	Asp	Asn	Pro	Glu	Ile 95	Val
Ala	Ala	His	Glu 100	Ala	Arg	Ile	Pro	Val 105	Ile	Arg	Arg	Ala	Glu 110	Met	Leu
Ala	Glu	Leu 115	Met	Arg	Phe	Arg	His 120	Gly	Ile	Ala	Ile	Ala 125	Gly	Thr	His
-	130					135					140	_		Glu	
145					150					155				Ala	160
			_	165					170					Ala 175	
		_	180					185					190	Ile	
		195			_		200			_		205	_	Phe	
	210					215					220			Phe	
225					230		_	_		235		_		Leu	240
	_		-	245					250					Asp 255	
_		_	260		_	_		265					270	His	
		275					280					285		Asn	
	290	_				295					300			Val	
305					310					315				Glu Pro	320
				325					330					335	
			340					345					350	Asp Arg	
-		355					360				_	365		_	
-	370		_	-		375					380			Arg Thr	
385				•	390					395				Ala	400
				405					410					415 Gly	
			420	_				425					430		
_	-	435	-				440		_			445		Ala	
	450					455	_				460			Gln	
465					470					475	ATG	GTÜ	TTG	Lys	480
гуз	Pro	GTIJ	Inr	485	Glu	GIU	GTII	GIN	н1S 490	Asp					

<210> 456 <211> 306

<212> PRT <213> Escherichia coli <400> 456 Met Thr Asp Lys Ile Ala Val Leu Leu Gly Gly Thr Ser Ala Glu Arg Glu Val Ser Leu Asn Ser Gly Ala Ala Val Leu Ala Gly Leu Arg Glu 25 Gly Gly Ile Asp Ala Tyr Pro Val Asp Pro Lys Glu Val Asp Val Thr Gln Leu Lys Ser Met Gly Phe Gln Lys Val Phe Ile Ala Leu His Gly Arg Gly Gly Glu Asp Gly Thr Leu Gln Gly Met Leu Glu Leu Met Gly Leu Pro Tyr Thr Gly Ser Gly Val Met Ala Ser Ala Leu Ser Met Asp 90 Lys Leu Arg Ser Lys Leu Leu Trp Gln Gly Ala Gly Leu Pro Val Ala 100 105 Pro Trp Val Ala Leu Thr Arg Ala Glu Phe Glu Lys Gly Leu Ser Asp 120 125 115 Lys Gln Leu Ala Glu Ile Ser Ala Leu Gly Leu Pro Val Ile Val Lys 135 . 140 Pro Ser Arg Glu Gly Ser Ser Val Gly Met Ser Lys Val Val Ala Glu 155 · 160 150 Asn Ala Leu Gln Asp Ala Leu Arg Leu Ala Phe Gln His Asp Glu Glu 165 170 Val Leu Ile Glu Lys Trp Leu Ser Gly Pro Glu Phe Thr Val Ala Ile 185 Leu Gly Glu Glu Ile Leu Pro Ser Ile Arg Ile Gln Pro Ser Gly Thr 200 Phe Tyr Asp Tyr Glu Ala Lys Tyr Leu Ser Asp Glu Thr Gln Tyr Phe 215 220 Cys Pro Ala Gly Leu Glu Ala Ser Gln Glu Ala Asn Leu Gln Ala Leu 230 235 Val Leu Lys Ala Trp Thr Thr Leu Gly Cys Lys Gly Trp Gly Arg Ile 245 250 Asp Val Met Leu Asp Ser Asp Gly Gln Phe Tyr Leu Leu Glu Ala Asn 265 Thr Ser Pro Gly Met Thr Ser His Ser Leu Val Pro Met Ala Ala Arg 280 Gln Ala Gly Met Ser Phe Ser Gln Leu Val Val Arq Ile Leu Glu Leu 295 300 Ala Asp 305 <210> 457 <211> 201 <212> PRT <213> Escherichia coli <400> 457 Met Ala Leu His Asp Glu Asn Val Val Trp His Ser His Pro Val Thr 10 Val Gln Gln Arg Glu Leu His His Gly His Arg Gly Val Val Leu Trp Phe Thr Gly Leu Ser Gly Ser Gly Lys Ser Thr Val Ala Gly Ala Leu 40

60

Glu Glu Ala Leu His Lys Leu Gly Val Ser Thr Tyr Leu Leu Asp Gly

Asp Asn Val Arg His Gly Leu Cys Ser Asp Leu Gly Phe Ser Asp Ala

70 Asp Arg Lys Glu Asn Ile Arg Arg Val Gly Glu Val Ala Asn Leu Met 90 Val Glu Ala Gly Leu Val Val Leu Thr Ala Phe Ile Ser Pro His Arg 100 105 Ala Glu Arg Gln Met Val Arg Glu Arg Val Gly Glu Gly Arg Phe Ile 120 Glu Val Phe Val Asp Thr Pro Leu Ala Ile Cys Glu Ala Arg Asp Pro 135 140 Lys Gly Leu Tyr Lys Lys Ala Arg Ala Gly Glu Leu Arg Asn Phe Thr 150 155 Gly Ile Asp Ser Val Tyr Glu Ala Pro Glu Ser Ala Glu Ile His Leu 165 170 Asn Gly Glu Gln Leu Val Thr Asn Leu Val Gln Gln Leu Leu Asp Leu 185 180 Leu Arg Gln Asn Asp Ile Ile Arg Ser

<210> 458

<211> 475

<212> PRT

<213> Escherichia coli

<400> 458

Met Asn Thr Ala Leu Ala Gln Gln Ile Ala Asn Glu Gly Val Glu Ala Trp Met Ile Ala Gln Gln His Lys Ser Leu Leu Arq Phe Leu Thr Cys Gly Ser Val Asp Asp Gly Lys Ser Thr Leu Ile Gly Arg Leu Leu 40 His Asp Thr Arg Gln Ile Tyr Glu Asp Gln Leu Ser Ser Leu His Asn 55 Asp Ser Lys Arg His Gly Thr Gln Gly Glu Lys Leu Asp Leu Ala Leu 70 75 Leu Val Asp Gly Leu Gln Ala Glu Arg Glu Gln Gly Ile Thr Ile Asp 90 Val Ala Tyr Arg Tyr Phe Ser Thr Glu Lys Arg Lys Phe Ile Ile Ala 100 105 Asp Thr Pro Gly His Glu Gln Tyr Thr Arg Asn Met Ala Thr Gly Ala 120 Ser Thr Cys Glu Leu Ala Ile Leu Leu Ile Asp Ala Arg Lys Gly Val 135 140 Leu Asp Gln Thr Arg Arg His Ser Phe Ile Ser Thr Leu Leu Gly Ile 150 155 Lys His Leu Val Val Ala Ile Asn Lys Met Asp Leu Val Asp Tyr Ser 165 170 Glu Glu Thr Phe Thr Arg Ile Arg Glu Asp Tyr Leu Thr Phe Ala Gly 185 Gln Leu Pro Gly Asn Leu Asp Ile Arg Phe Val Pro Leu Ser Ala Leu 200 Glu Gly Asp Asn Val Ala Ser Gln Ser Glu Ser Met Pro Trp Tyr Ser 215 220 Gly Pro Thr Leu Leu Glu Val Leu Glu Thr Val Glu Ile Gln Arg Val 230 235 Val Asp Ala Gln Pro Met Arg Phe Pro Val Gln Tyr Val Asn Arg Pro 250 Asn Leu Asp Phe Arg Gly Tyr Ala Gly Thr Leu Ala Ser Gly Arg Val 265 270 Glu Val Gly Gln Arg Val Lys Val Leu Pro Ser Gly Val Glu Ser Asn 280

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Val Ala Arg Ile Val Thr Phe Asp Gly Asp Arg Glu Glu Ala Phe Ala
                       295
Gly Glu Ala Ile Thr Leu Val Leu Thr Asp Glu Ile Asp Ile Ser Arg
                   310
                                       315
Gly Asp Leu Leu Ala Ala Asp Glu Ala Leu Pro Ala Val Gln Ser
              325
                                   330
Ala Ser Val Asp Val Val Trp Met Ala Glu Gln Pro Leu Ser Pro Gly
                               345
Gln Ser Tyr Asp Ile Lys Ile Ala Gly Lys Lys Thr Arg Ala Arg Val
       355
                           360
                                               365
Asp Gly Ile Arg Tyr Gln Val Asp Ile Asn Asn Leu Thr Gln Arg Glu
                                          380
                      375
Val Glu Asn Leu Pro Leu Asn Gly Ile Gly Leu Val Asp Leu Thr Phe
                   390
                                       395
Asp Glu Pro Leu Val Leu Asp Arg Tyr Gln Gln Asn Pro Val Thr Gly
               405
                                   410
Gly Leu Ile Phe Ile Asp Arg Leu Ser Asn Val Thr Val Gly Ala Gly
                               425
                                                   430
Met Val His Glu Pro Val Ser Gln Ala Thr Ala Ala Pro Ser Glu Phe
                           440
                                              445
       435
Ser Ala Phe Glu Leu Glu Leu Asn Ala Leu Val Arg Arg His Phe Pro
                       455
His Trp Gly Ala Arg Asp Leu Leu Gly Asp Lys
                   470
<210> 459
<211> 127
<212> PRT
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<213> Escherichia coli

### <400> 459

Met Arg His Arg Lys Ser Gly Arg Gln Leu Asn Arg Asn Ser Ser His 10 Arg Gln Ala Met Phe Arg Asn Met Ala Gly Ser Leu Val Arg His Glu 25 Ile Ile Lys Thr Thr Leu Pro Lys Ala Lys Glu Leu Arg Arg Val Val 40 45 Glu Pro Leu Ile Thr Leu Ala Lys Thr Asp Ser Val Ala Asn Arg Arg 55 Leu Ala Phe Ala Arg Thr Arg Asp Asn Glu Ile Val Ala Lys Leu Phe 70 Asn Glu Leu Gly Pro Arg Phe Ala Ser Arg Ala Gly Gly Tyr Thr Arg 90 Ile Leu Lys Cys Gly Phe Arg Ala Gly Asp Asn Ala Pro Met Ala Tyr 100 105 110 Ile Glu Leu Val Asp Arg Ser Glu Lys Ala Glu Ala Ala Glu 120

<210> 460

<211> 329

<212> PRT

<213> Escherichia coli

### <400> 460

 Met Gln Gly Ser Val Thr Glu Phe Leu Lys Pro Arg Leu Val Asp Ile

 1
 5

 Glu Gln Val Ser Ser Thr His Ala Lys Val Thr Leu Glu Pro Leu Glu

 20
 25

 Arg Gly Phe Gly His Thr Leu Gly Asn Ala Leu Arg Arg Ile Leu Leu

Ser Ser Met Pro Gly Cys Ala Val Thr Glu Val Glu Ile Asp Gly Val Leu His Glu Tyr Ser Thr Lys Glu Gly Val Gln Glu Asp Ile Leu Glu 70 Ile Leu Leu Asn Leu Lys Gly Leu Ala Val Arg Val Gln Gly Lys Asp 90 Glu Val Ile Leu Thr Leu Asn Lys Ser Gly Ile Gly Pro Val Thr Ala 105 Ala Asp Ile Thr His Asp Gly Asp Val Glu Ile Val Lys Pro Gln His 120 Val Ile Cys His Leu Thr Asp Glu Asn Ala Ser Ile Ser Met Arg Ile 135 Lys Val Gln Arg Gly Arg Gly Tyr Val Pro Ala Ser Thr Arg Ile His 150 155 Ser Glu Glu Asp Glu Arg Pro Ile Gly Arg Leu Leu Val Asp Ala Cys 165 170 Tyr Ser Pro Val Glu Arg Ile Ala Tyr Asn Val Glu Ala Ala Arg Val 180 185 Glu Gln Arg Thr Asp Leu Asp Lys Leu Val Ile Glu Met Glu Thr Asn 200 Gly Thr Ile Asp Pro Glu Glu Ala Ile Arg Arg Ala Ala Thr Ile Leu 215 220 Ala Glu Gln Leu Glu Ala Phe Val Asp Leu Arg Asp Val Arg Gln Pro 230 235 Glu Val Lys Glu Glu Lys Pro Glu Phe Asp Pro Ile Leu Leu Arg Pro 245 250 Val Asp Asp Leu Glu Leu Thr Val Arg Ser Ala Asn Cys Leu Lys Ala 265 Glu Ala Ile His Tyr Ile Gly Asp Leu Val Gln Arg Thr Glu Val Glu 280 Leu Leu Lys Thr Pro Asn Leu Gly Lys Lys Ser Leu Thr Glu Ile Lys 295 Asp Val Leu Ala Ser Arg Gly Leu Ser Leu Gly Met Arg Leu Glu Asn 310 Trp Pro Pro Ala Ser Ile Ala Asp Glu 325

<210> 461

<211> 206

<212> PRT

<213> Escherichia coli

<400> 461

Met Ala Arg Tyr Leu Gly Pro Lys Leu Lys Leu Ser Arg Arg Glu Gly 10 Thr Asp Leu Phe Leu Lys Ser Gly Val Arg Ala Ile Asp Thr Lys Cys 25 Lys Ile Glu Gln Ala Pro Gly Gln His Gly Ala Arg Lys Pro Arg Leu 40 Ser Asp Tyr Gly Val Gln Leu Arg Glu Lys Gln Lys Val Arg Arg Ile 55 Tyr Gly Val Leu Glu Arg Gln Phe Arg Asn Tyr Tyr Lys Glu Ala Ala 75 70 Arg Leu Lys Gly Asn Thr Gly Glu Asn Leu Leu Ala Leu Leu Glu Gly 90 Arg Leu Asp Asn Val Val Tyr Arg Met Gly Phe Gly Ala Thr Arg Ala 105 Glu Ala Arg Gln Leu Val Ser His Lys Ala Ile Met Val Asn Gly Arg

 Val
 Val
 Asn
 Ile
 Ala
 Ser
 Tyr
 Gln
 Val
 Ser
 Pro
 Asn
 Asp
 Val
 Val
 Ser

 11e
 Arg
 Glu
 Lys
 Ala
 Lys
 Gln
 Ser
 Arg
 Val
 Lys
 Ala
 Ala
 Leu
 Glu
 Glu
 Leu
 Glu
 Leu
 Glu
 Leu
 Glu
 Leu
 Glu
 Ala
 Glu
 Glu
 Intraction
 Intractio

<210> 462

<211> 129

<212> PRT

<213> Escherichia coli

<400> 462

 Met
 Ala
 Lys
 Ala
 Pro
 Ile
 Arg
 Ala
 Arg
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 Gln
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 Ile
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 Ile
 Ile
 Ile
 Ile
 Ala
 Ser
 Phe
 Asn
 Asn
 Thr
 Ile
 Val
 Ala
 His
 Ile
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 Ala
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 Phe
 Asn
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 Ala
 Ile
 Ile
 Ala
 Ala
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Val

<210> 463

<211> 118

<212> PRT

<213> Escherichia coli

<400> 463

 Met
 Ala
 Arg
 Ile
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 Gly
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 Lys
 His
 Ala
 Val

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 Ala
 Leu
 Thr
 Ser
 Ile
 Tyr
 Gly
 Val
 Gly
 Lys
 Thr
 Arg
 Ser
 Lys
 Ala

 Ile
 Leu
 Ala
 Ala
 Gly
 Ile
 Ala
 Glu
 Asp
 Val
 Lys
 Ile
 Ser
 Glu
 Leu

 Ser
 Glu
 Gly
 Gly
 Ile
 Ala
 Glu
 Asp
 Val
 Ala
 Lys
 Ile
 Leu

 Ser
 Glu
 Gly
 Gly
 Ile
 Ala
 Gly
 Asp
 Glu
 Val
 Ala
 Lys
 Phe
 Val

 Ser
 Glu
 Gly
 Asp
 Leu
 Arg
 Gly
 Leu
 Arg
 Ile
 Ser
 Het
 Ser
 Ile
 Lys
 Arg
 Leu

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 Arg
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 Ile
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 Ile
 I

105

Arg Lys Pro Ile Lys Lys

115

<210> 464 <211> 460 <212> PRT <213> Escherichia coli Met Thr Gln Leu Thr Met Lys Asp Lys Ile Gly Tyr Gly Leu Gly Asp Thr Ala Cys Gly Phe Val Trp Gln Ala Thr Met Phe Leu Leu Ala Tyr Phe Tyr Thr Asp Val Phe Gly Leu Ser Ala Gly Ile Met Gly Thr Leu Phe Leu Val Ser Arg Val Leu Asp Ala Val Thr Asp Pro Leu Met Gly Leu Leu Val Asp Arg Thr Arg Thr Arg His Gly Gln Phe Arg Pro Phe 70 Leu Leu Trp Gly Ala Ile Pro Phe Gly Ile Val Cys Val Leu Thr Phe 90 Tyr Thr Pro Asp Phe Ser Ala Gln Gly Lys Ile Ile Tyr Ala Cys Val 105 Thr Tyr Ile Leu Leu Thr Leu Val Tyr Thr Phe Val Asn Val Pro Tyr 120 Cys Ala Met Pro Gly Val Ile Thr Ala Asp Pro Lys Glu Arg His Ala 135 140 Leu Gln Ser Trp Arg Phe Phe Leu Ala Ala Ala Gly Ser Leu Ala Ile 150 155 Ser Gly Ile Ala Leu Pro Leu Val Ser Ile Ile Gly Lys Gly Asp Glu 170 165 Gln Val Gly Tyr Phe Gly Ala Met Cys Val Leu Gly Leu Ser Gly Val 185 Val Leu Leu Tyr Val Cys Phe Phe Thr Thr Lys Glu Arg Tyr Thr Phe 200 Glu Val Gln Pro Gly Ser Ser Val Ala Lys Asp Leu Lys Leu Leu 215 Gly Asn Ser Gln Trp Arg Ile Met Cys Ala Phe Lys Met Met Ala Thr 230 235 Cys Ser Asn Val Val Arg Gly Gly Ala Thr Leu Tyr Phe Val Lys Tyr 250 245 Val Met Asp His Pro Glu Leu Ala Thr Gln Phe Leu Leu Tyr Gly Ser 265 260 Leu Ala Thr Met Phe Gly Ser Leu Cys Ser Ser Arg Leu Leu Gly Arg 280 Phe Asp Arg Val Thr Ala Phe Lys Trp Ile Ile Val Ala Tyr Ser Leu 295 Ile Ser Leu Leu Ile Phe Val Thr Pro Ala Glu His Ile Ala Leu Ile 315 310 Phe Ala Leu Asn Ile Leu Phe Leu Phe Val Phe Asn Thr Thr Pro 330 325 Leu Gln Trp Leu Met Ala Ser Asp Val Val Asp Tyr Glu Glu Ser Arg 345 Ser Gly Arg Arg Leu Asp Gly Leu Val Phe Ser Thr Tyr Leu Phe Ser 360 Leu Lys Ile Gly Leu Ala Ile Gly Gly Ala Val Val Gly Trp Ile Leu 375 Ala Tyr Val Asn Tyr Ser Ala Ser Ser Ser Val Gln Pro Val Glu Val 390 395 Leu Thr Thr Ile Lys Ile Leu Phe Cys Val Val Pro Val Val Leu Tyr 410 405 Ala Gly Met Phe Ile Met Leu Ser Leu Tyr Lys Leu Thr Asp Ala Arg

425

420

Val Glu Ala Ile Ser Arg Gln Leu Ile Lys His Arg Ala Ala Gln Gly
435 440 445

Glu Ala Val Pro Asp Ala Ala Thr Ala Ala Ser His
450 455 460

<210> 465 <211> 536 <212> PRT <213> Escherichia coli

<400> 465

Met Glu Ile Thr Asn Pro Ile Leu Thr Gly Phe Asn Pro Asp Pro Ser 10 Leu Cys Arg Gln Gly Glu Asp Tyr Tyr Ile Ala Thr Ser Thr Phe Glu Trp Phe Pro Gly Val Arg Ile Tyr His Ser Arg Asp Leu Lys Asn Trp 40 Ser Leu Val Ser Thr Pro Leu Asp Arg Val Ser Met Leu Asp Met Lys 55 Gly Asn Pro Asp Ser Gly Gly Ile Trp Ala Pro Cys Leu Ser Tyr Ala 70 Asp Gly Lys Phe Trp Leu Leu Tyr Thr Asp Val Lys Ile Val Asp Ser 90 Pro Trp Lys Asn Gly Arg Asn Phe Leu Val Thr Ala Pro Ser Ile Glu 105 Gly Pro Trp Ser Glu Pro Ile Pro Met Gly Asn Gly Gly Phe Asp Pro 120 Ser Leu Phe His Asp Asp Asp Gly Arg Lys Tyr Tyr Ile Tyr Arg Pro 135 140 Trp Gly Pro Arg His His Ser Asn Pro His Asn Thr Ile Val Leu Gln 155 150 Ala Phe Asp Pro Gln Thr Gly Thr Leu Ser Pro Glu Arg Lys Thr Leu 165 170 Phe Thr Gly Thr Pro Leu Cys Tyr Thr Glu Gly Ala His Leu Tyr Arg 185 180 His Ala Gly Trp Tyr Tyr Leu Met Ala Ala Glu Gly Gly Thr Ser Tyr 200 205 Glu His Ala Val Val Leu Arg Ser Lys Asn Ile Asp Gly Pro Tyr 215 Glu Leu His Pro Asp Val Thr Met Met Thr Ser Trp His Leu Pro Glu 230 235 Asn Pro Leu Gln Lys Ser Gly His Gly Ser Leu Leu Gln Thr His Thr 250 . 255 245 Gly Glu Trp Tyr Met Ala Tyr Leu Thr Ser Arg Pro Leu Arg Leu Pro 260 265 270 Gly Val Pro Leu Leu Ala Ser Gly Gly Arg Gly Tyr Cys Pro Leu Gly 275 280 285 Arg Glu Thr Gly Ile Ala Arg Ile Glu Trp Arg Asp Gly Trp Pro Tyr 295 300 Val Glu Gly Gly Lys His Ala Gln Leu Thr Val Lys Gly Pro Gln Val 315 310 Ala Glu Gln Pro Ala Ala Val Pro Gly Asn Trp Arg Asp Phe Asp 330 Ala Ser Ser Leu Asp Pro Glu Leu Gln Thr Leu Arg Ile Pro Phe Asp 345 Asp Thr Leu Gly Ser Leu Thr Ala Arg Pro Gly Phe Leu Arg Leu Tyr 360 Gly Asn Asp Ser Leu Asn Ser Thr Phe Thr Gln Ser Thr Val Ala Arg 375 380 . . Arg Trp Gln His Phe Ala Phe Arg Ala Glu Thr Arg Met Glu Phe Ser

PCT/US00/34419

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WO 01/48209
                   390
                                       395
Pro Val His Phe Gln Gln Ser Ala Gly Leu Thr Cys Tyr Tyr Asn Ser
                                   410
Lys Asn Trp Ser Tyr Cys Phe Val Asp Tyr Glu Glu Gly Gln Gly Arg
                               425
Thr Ile Lys Val Ile Gln Leu Asp His Asn Val Pro Ser Trp Pro Leu
                          440
His Glu Gln Pro Ile Pro Val Pro Glu His Ala Glu Ser Val Trp Leu
                       455
                                          460
Arg Val Asp Val Asp Thr Leu Val Tyr Arg Tyr Ser Tyr Ser Phe Asp
                   470
                                       475
Gly Glu Thr Trp His Thr Val Pro Val Thr Tyr Glu Ala Trp Lys Leu
               485
                                   490
Ser Asp Asp Tyr Ile Gly Gly Arg Gly Phe Phe Thr Gly Ala Phe Val
           500
                               505
Gly Leu His Cys Glu Asp Ile Ser Gly Asp Gly Cys Tyr Ala Asp Phe
      515
                       520
Asp Tyr Phe Thr Tyr Glu Pro Val
  530
<210> 466
<211> 325
<212> PRT
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<400> 466
Met His Met Lys Lys Ile Ile Phe Ala Phe Ile Ile Leu Phe Val Phe
Leu Leu Pro Met Ile Ile Phe Tyr Gln Pro Trp Val Asn Ala Leu Pro
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Ser Thr Pro Arg His Ala Ser Pro Glu Gln Leu Glu Lys Thr Val Arg
                           40
Tyr Leu Thr Gln Thr Val His Pro Arg Ser Ala Asp Asn Ile Asp Asn
                       55
Leu Asn Arg Ser Ala Glu Tyr Ile Lys Glu Val Phe Val Ser Ser Gly
                   70
                                       75
Ala Arg Val Thr Ser Gln Asp Val Pro Ile Thr Gly Gly Pro Tyr Lys
                                  90
              85
Asn Ile Val Ala Asp Tyr Gly Pro Ala Asp Gly Pro Leu Ile Ile Ile
                              105
Gly Ala His Tyr Asp Ser Ala Ser Ser Tyr Glu Asn Asp Gln Leu Thr
                          120
                                              125
Tyr Thr Pro Gly Ala Asp Asp Asn Ala Ser Gly Val Ala Gly Leu Leu
                       135
                                           140
Glu Leu Ala Arg Leu Leu His Gln Gln Val Pro Lys Thr Gly Val Gln
                   150
                                       155
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Leu Val Ala Tyr Ala Ser Glu Glu Pro Pro Phe Phe Arg Ser Asp Glu 165 170 Met Gly Ser Ala Val His Ala Ala Ser Leu Glu Arg Pro Val Lys Leu 185 Met Ile Ala Leu Glu Met Ile Gly Tyr Tyr Asp Ser Ala Pro Gly Ser 200 Gln Asn Tyr Pro Tyr Pro Ala Met Ser Trp Leu Tyr Pro Asp Arg Gly 215 220 Asp Phe Ile Ala Val Val Gly Arg Ile Gln Asp Ile Asn Ala Val Arg 230 235 Gln Val Lys Ala Ala Leu Leu Ser Ser Gln Asp Leu Ser Val Tyr Ser 250 245 Met Asn Thr Pro Gly Phe Ile Pro Gly Ile Asp Phe Ser Asp His Leu

Asn Tyr Trp Gln His Asp Ile Pro Ala Ile Met Ile Thr Asp Thr Ala 275

Phe Tyr Arg Asn Lys Gln Tyr His Leu Pro Gly Asp Thr Ala Asp Arg 290

Leu Asn Tyr Gln Lys Met Ala Gln Val Val Asp Gly Val Ile Thr Leu 305

Leu Tyr Asn Ser Lys 325

<210> 467 <211> 320 <212> PRT <213> Escherichia coli

<400> 467

Met Met Ile Lys Thr Arg Phe Ser Arg Trp Leu Thr Phe Phe Thr Phe 10 Ala Ala Ala Val Ala Leu Ala Leu Pro Ala Lys Ala Asn Thr Trp Pro Leu Pro Pro Ala Gly Ser Arg Leu Val Gly Glu Asn Lys Phe His Val 40 Val Glu Asn Asp Gly Gly Ser Leu Glu Ala Ile Ala Lys Lys Tyr Asn 55 Val Gly Phe Leu Ala Leu Leu Gln Ala Asn Pro Gly Val Asp Pro Tyr 75 Val Pro Arg Ala Gly Ser Val Leu Thr Ile Pro Leu Gln Thr Leu Leu 90 Pro Asp Ala Pro Arg Glu Gly Ile Val Ile Asn Ile Ala Glu Leu Arg 105 Leu Tyr Tyr Tyr Pro Pro Gly Lys Asn Ser Val Thr Val Tyr Pro Ile 120 Gly Ile Gly Gln Leu Gly Gly Asp Thr Leu Thr Pro Thr Met Val Thr 135 140 Thr Val Ser Asp Lys Arg Ala Asn Pro Thr Trp Thr Pro Thr Ala Asn 150 155 Ile Arg Ala Arg Tyr Lys Ala Gln Gly Ile Glu Leu Pro Ala Val Val 165 170 Pro Ala Gly Leu Asp Asn Pro Met Gly His His Ala Ile Arg Leu Ala 180 185 Ala Tyr Gly Gly Val Tyr Leu Leu His Gly Thr Asn Ala Asp Phe Gly . 200 Ile Gly Met Arg Val Ser Ser Gly Cys Ile Arg Leu Arg Asp Asp Asp 210 215 Ile Lys Thr Leu Phe Ser Gln Val Thr Pro Gly Thr Lys Val Asn Ile 235 230 Ile Asn Thr Pro Ile Lys Val Ser Ala Glu Pro Asn Gly Ala Arg Leu 250 Val Glu Val His Gln Pro Leu Ser Glu Lys Ile Asp Asp Pro Gln 265 260 · Leu Leu Pro Ile Thr Leu Asn Ser Ala Met Gln Ser Phe Lys Asp Ala 280 Ala Gln Thr Asp Ala Glu Val Met Gln His Val Met Asp Val Arg Ser 300 290 . 295 Gly Met Pro Val Asp Val Arg Arg His Gln Val Ser Pro Gln Thr Leu 315

<210> 468 <211> 494 <212> PRT

### <213> Escherichia coli

<400> 468 Met Val Ala Ile His Leu Leu Pro Val Ser Tyr Asn Ser Ala Thr Ser Thr Val Asn Ile Ser Ala Arg Ile Ile Pro Leu Leu Ile Ile His Gln Arg Tyr Lys Ile Pro Met Pro Lys Val Gln Ala Asp Gly Leu Pro Leu 40 Pro Gln Arg Tyr Gly Ala Ile Leu Thr Ile Val Ile Gly Ile Ser Met 55 Ala Val Leu Asp Gly Ala Ile Ala Asn Val Ala Leu Pro Thr Ile Ala 70 Thr Asp Leu His Ala Thr Pro Ala Ser Ser Ile Trp Val Val Asn Ala 90 Tyr Gln Ile Ala Ile Val Ile Ser Leu Leu Ser Phe Ser Phe Leu Gly 105 Asp Met Phe Gly Tyr Arg Arg Ile Tyr Lys Cys Gly Leu Val Val Phe 120 Leu Leu Ser Ser Leu Phe Cys Ala Leu Ser Asp Ser Leu Gln Met Leu 135 Thr Leu Ala Arg Val Ile Gln Gly Phe Gly Gly Ala Ala Leu Met Ser 150 155 Val Asn Thr Ala Leu Ile Arg Leu Ile Tyr Pro Gln Arg Phe Leu Gly 165 170 Arg Gly Met Gly Ile Asn Ser Phe Ile Val Ala Val Ser Ser Ala Ala 185 180 Gly Pro Thr Ile Ala Ala Ala Ile Leu Ser Ile Ala Ser Trp Lys Trp 200 Leu Phe Leu Ile Asn Val Pro Leu Gly Ile Ile Ala Leu Leu Leu Ala 215 Met Arg Phe Leu Pro Pro Asn Gly Ser Arg Ala Ser Lys Pro Arg Phe 230 235 Asp Leu Pro Ser Ala Val Met Asn Ala Leu Thr Phe Gly Leu Leu Ile 245 250 Thr Ala Leu Ser Gly Phe Ala Gln Gly Gln Ser Leu Thr Leu Ile Ala 265 Ala Glu Leu Val Val Met Val Val Val Gly Ile Phe Phe Ile Arg Arg 280 Gln Leu Ser Leu Pro Val Pro Leu Leu Pro Val Asp Leu Leu Arg Ile 295 Pro Leu Phe Ser Leu Ser Ile Cys Thr Ser Val Cys Ser Phe Cys Ala 310 315 Gln Met Leu Ala Met Val Ser Leu Pro Phe Tyr Leu Gln Thr Val Leu 330 Gly Arg Ser Glu Val Glu Thr Gly Leu Leu Thr Pro Trp Pro Leu 345 Ala Thr Met Val Met Ala Pro Leu Ala Gly Tyr Leu Ile Glu Arg Val 360 His Ala Gly Leu Leu Gly Ala Leu Gly Leu Phe Ile Met Ala Ala Gly 375 Leu Phe Ser Leu Val Leu Leu Pro Ala Ser Pro Ala Asp Ile Asn Ile 395 Ile Trp Pro Met Ile Leu Cys Gly Ala Gly Phe Gly Leu Phe Gln Ser 410 Pro Asn Asn His Thr Ile Ile Thr Ser Ala Pro Arg Glu Arg Ser Gly 425 Gly Ala Ser Gly Met Leu Gly Thr Ala Arg Leu Leu Gly Gln Ser Ser 440 Gly Ala Ala Leu Val Ala Leu Met Leu Asn Gln Phe Gly Asp Asn Gly

Thr His Val Ser Leu Met Ala Ala Ala Ile Leu Ala Val Ile Ala Ala 465 470 475 480

Cys Val Ser Gly Leu Arg Ile Thr Gln Pro Arg Ser Arg Ala 485 490

<210> 469 <211> 477 <212> PRT <213> Escherichia coli <400> 469 Met Lys Val Thr Leu Pro Glu Phe Glu Arg Ala Gly Val Met Val Val Gly Asp Val Met Leu Asp Arg Tyr Trp Tyr Gly Pro Thr Ser Arg Ile 25 Ser Pro Glu Ala Pro Val Pro Val Val Lys Val Asn Thr Ile Glu Glu Arg Pro Gly Gly Ala Ala Asn Val Ala Met Asn Ile Ala Ser Leu Gly 55 Ala Asn Ala Arg Leu Val Gly Leu Thr Gly Ile Asp Asp Ala Ala Arg 75 80 70 Ala Leu Ser Lys Ser Leu Ala Asp Val Asn Val Lys Cys Asp Phe Val 90 95 Ser Val Pro Thr His Pro Thr Ile Thr Lys Leu Arg Val Leu Ser Arg 105 Asn Gln Gln Leu Ile Arg Leu Asp Phe Glu Glu Gly Phe Glu Gly Val 120 Asp Pro Gln Pro Leu His Glu Arg Ile Asn Gln Ala Leu Ser Ser Ile 135 140 Gly Ala Leu Val Leu Ser Asp Tyr Ala Lys Gly Ala Leu Ala Ser Val 150 155 Gln Gln Met Ile Gln Leu Ala Arg Lys Ala Gly Val Pro Val Leu Ile 170 Asp Pro Lys Gly Thr Asp Phe Glu Arg Tyr Arg Gly Ala Thr Leu Leu 185 Thr Pro Asn Leu Ser Glu Phe Glu Ala Val Val Gly Lys Cys Lys Thr 200 205 Glu Glu Glu Ile Val Glu Arg Gly Met Lys Leu Ile Ala Asp Tyr Glu 215 . 220 Leu Ser Ala Leu Leu Val Thr Arg Ser Glu Gln Gly Met Ser Leu Leu 235 230 Gln Pro Gly Lys Ala Pro Leu His Met Pro Thr Gln Ala Gln Glu Val 245 250 Tyr Asp Val Thr Gly Ala Gly Asp Thr Val Ile Gly Val Leu Ala Ala 265 . Thr Leu Ala Ala Gly Asn Ser Leu Glu Glu Ala Cys Phe Phe Ala Asn 280 285 Ala Ala Ala Gly Val Val Val Gly Lys Leu Gly Thr Ser Thr Val Ser 295 300 . . Pro Ile Glu Leu Glu Asn Ala Val Arg Gly Arg Ala Asp Thr Gly Phe 315 . 310 Gly Val Met Thr Glu Glu Glu Leu Lys Leu Ala Val Ala Ala Ala Arg 325 330 Lys Arg Gly Glu Lys Val Val Met Thr Asn Gly Val Phe Asp Ile Leu -345 His Ala Gly His Val Ser Tyr Leu Ala Asn Ala Arg Lys Leu Gly Asp 360 365 Arg Leu Ile Val Ala Val Asn Ser Asp Ala Ser Thr Lys Arg Leu Lys 375 380 Gly Asp Ser Arg Pro Val Asn Pro Leu Glu Gln Arg Met Ile Val Leu PCT/US00/34419

WO 01/48209 390 395 Gly Ala Leu Glu Ala Val Asp Trp Val Val Ser Phe Glu Glu Asp Thr 405 410 Pro Gln Arg Leu Ile Ala Gly Ile Leu Pro Asp Leu Leu Val Lys Gly 425 Gly Asp Tyr Lys Pro Glu Glu Ile Ala Gly Ser Lys Glu Val Trp Ala 440 Asn Gly Gly Glu Val Leu Val Leu Asn Phe Glu Asp Gly Cys Ser Thr 455 Thr Asn Ile Ile Lys Lys Ile Gln Gln Asp Lys Lys Gly 470 <210> 470 <211> 946 <212> PRT <213> Escherichia coli <400> 470 Met Lys Pro Leu Ser Ser Pro Leu Gln Gln Tyr Trp Gln Thr Val Val 10 Glu Arg Leu Pro Glu Pro Leu Ala Glu Glu Ser Leu Ser Ala Gln Ala 25 Lys Ser Val Leu Thr Phe Ser Asp Phe Val Gln Asp Ser Val Ile Ala 40 His Pro Glu Trp Leu Thr Glu Leu Glu Ser Gln Pro Pro Gln Ala Asp 55 Glu Trp Gln His Tyr Ala Ala Trp Leu Gln Glu Ala Leu Cys Asn Val

70 7.5 Ser Asp Glu Ala Gly Leu Met Arg Glu Leu Arg Leu Phe Arg Arg Arg 90 Ile Met Val Arg Ile Ala Trp Ala Gln Thr Leu Ala Leu Val Thr Glu 105 Glu Ser Ile Leu Gln Gln Leu Ser Tyr Leu Ala Glu Thr Leu Ile Val 120 Ala Ala Arg Asp Trp Leu Tyr Asp Ala Cys Cys Arg Glu Trp Gly Thr . 135 Pro Cys Asn Ala Gln Gly Glu Ala Gln Pro Leu Leu Ile Leu Gly Met 150 155 Gly Lys Leu Gly Gly Gly Glu Leu Asn Phe Ser Ser Asp Ile Asp Leu 170 Ile Phe Ala Trp Pro Glu His Gly Cys Thr Gln Gly Gly Arg Arg Glu 185 Leu Asp Asn Ala Gln Phe Phe Thr Arg Met Gly Gln Arg Leu Ile Lys 200 Val Leu Asp Gln Pro Thr Gln Asp Gly Phe Val Tyr Arg Val Asp Met 215 220 Arg Leu Arg Pro Phe Gly Glu Ser Gly Pro Leu Val Leu Ser Phe Ala 230 235 Ala Leu Glu Asp Tyr Tyr Gln Glu Gln Gly Arg Asp Trp Glu Arg Tyr 250 245 Ala Met Val Lys Ala Arg Ile Met Gly Asp Ser Glu Gly Val Tyr Ala 265 260 Asn Glu Leu Arg Ala Met Leu Arg Pro Phe Val Phe Arg Arg Tyr Ile

Asp Phe Ser Val Ile Gln Ser Leu Arg Asn Met Lys Gly Met Ile Ala 295 300 Arg Glu Val Arg Arg Arg Gly Leu Thr Asp Asn Ile Lys Leu Gly Ala 315 310 Gly Gly Ile Arg Glu Ile Glu Phe Ile Val Gln Val Phe Gln Leu Ile 330 325

280

Arg Gly Gly Arg Glu Pro Ser Leu Gln Ser Arg Ser Leu Leu Pro Thr 345 Leu Ser Ala Ile Ala Glu Leu His Leu Leu Ser Glu Asn Asp Ala Glu 360 Gln Leu Arg Val Ala Tyr Leu Phe Leu Arg Arg Leu Glu Asn Leu Leu 375 380 Gln Ser Ile Asn Asp Glu Gln Thr Gln Thr Leu Pro Ser Asp Glu Leu 390 395 Asn Arg Ala Arg Leu Ala Trp Ala Met Asp Phe Ala Asp Trp Pro Gln 405 410 Leu Thr Gly Ala Leu Thr Ala His Met Thr Asn Val Arg Arg Val Phe 425 Asn Glu Leu Ile Gly Asp Asp Glu Ser Glu Thr Gln Glu Glu Ser Leu 440 Ser Glu Gln Trp Arg Glu Leu Trp Gln Asp Ala Leu Gln Glu Asp Asp 455 460 Thr Thr Pro Val Leu Ala His Leu Ser Glu Asp Asp Arg Lys Gln Val 475 470 Leu Thr Leu Ile Ala Asp Phe Arg Lys Glu Leu Asp Lys Arg Thr Ile 490 495 485 Gly Pro Arg Gly Arg Gln Val Leu Asp His Leu Met Pro His Leu Leu 505 500 Ser Asp Val Cys Ala Arg Glu Asp Ala Ala Val Thr Leu Ser Arg Ile 520 Thr Ala Leu Leu Val Gly Ile Val Thr Arg Thr Thr Tyr Leu Glu Leu 540 535 Leu Ser Glu Phe Pro Ala Ala Leu Lys His Leu Ile Ser Leu Cys Ala 555 550 Ala Ser Pro Met Ile Ala Ser Gln Leu Ala Arg Tyr Pro Leu Leu 565 570 Asp Glu Leu Leu Asp Pro Asn Thr Leu Tyr Gln Pro Thr Ala Thr Asp 585 580 Ala Tyr Arg Asp Glu Leu Arg Gln Tyr Leu Leu Arg Val Pro Glu Asp 600 595 Asp Glu Glu Gln Gln Leu Glu Ala Leu Arg Gln Phe Lys Gln Ala Gln 615 620 Leu Leu Arg Ile Ala Ala Ala Asp Ile Ala Gly Thr Leu Pro Val Met 635 630 Lys Val Ser Asp His Leu Thr Trp Leu Ala Glu Ala Met Ile Asp Ala 650 645 Val Val Gln Gln Ala Trp Val Gln Met Val Ala Arg Tyr Gly Lys Pro 665 670 Asn His Leu Asn Glu Arg Glu Gly Arg Gly Phe Ala Val Val Gly Tyr 680 Gly Lys Leu Gly Gly Trp Glu Leu Gly Tyr Ser Ser Asp Leu Asp Leu 695 Ile Phe Leu His Asp Cys Pro Met Asp Ala Met Thr Asp Gly Glu Arg 715 710 Glu Ile Asp Gly Arg Gln Phe Tyr Leu Arg Leu Ala Gln Arg Ile Met 725 730 His Leu Phe Ser Thr Arg Thr Ser Ser Gly Ile Leu Tyr Glu Val Asp 740 . 745 Ala Arg Leu Arg Pro Ser Gly Ala Ala Gly Met Leu Val Thr Ser Ala 765 760 Glu Ala Phe Ala Asp Tyr Gln Lys Asn Glu Ala Trp Thr Trp Glu His 775 Gln Ala Leu Val Arg Ala Arg Val Val Tyr Gly Asp Pro Gln Leu Thr 795 790 Ala His Phe Asp Ala Val Arg Arg Glu Ile Met Thr Leu Pro Arg Glu 810 805 Gly Lys Thr Leu Gln Thr Glu Val Arg Glu Met Arg Glu Lys Met Arg

825 Ala His Leu Gly Asn Lys His Arg Asp Arg Phe Asp Ile Lys Ala Asp 840 Glu Gly Gly Ile Thr Asp Ile Glu Phe Ile Thr Gln Tyr Leu Val Leu 855 860 Arg Tyr Ala His Glu Lys Pro Lys Leu Thr Arg Trp Ser Asp Asn Val 870 875 Arg Ile Leu Glu Leu Leu Ala Gln Asn Asp Ile Met Glu Glu Glu Glu 885 890 Ala Met Ala Leu Thr Arg Ala Tyr Thr Thr Leu Arg Asp Glu Leu His 905 His Leu Ala Leu Gln Glu Leu Pro Gly His Val Ser Glu Asp Cys Phe 920 Thr Ala Glu Arg Glu Leu Val Arg Ala Ser Trp Gln Lys Trp Leu Val 935 940 Glu Glu 945

<210> 471

<211> 433

<212> PRT

<213> Escherichia coli

<400> 471

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Ala Thr Ile Ala Ser Ala Val Ser Ala Val Thr Ala Val Tyr Ser Thr 295 Glu Thr Ala Met Ala Lys Leu Ala Leu Thr Glu Trp Leu Val Ser Lys 315 310 Ala Trp Gln Pro Phe Leu Asp Ala Lys Ala Gln Gly Lys Ile Ser Asp 330 Ser Phe Lys Arg Phe Ala Asp Ile His Leu Ser Arg His Ala Ala Glu 345 Leu Lys Ser Val Phe Cys Gln Pro Leu Gly Asp Arg Tyr Arg Asp Gln 360 Leu Pro Arg Leu Thr Arg Asp Ile Asp Ser Ile Leu Leu Leu Ala Gly 375 Tyr Tyr Asp Pro Val Val Ala Gln Ala Trp Leu Glu Asn Trp Gln Gly 395 390 Leu His His Ala Ile Ala Thr Gly Gln Arg Ile Glu Ile Glu His Phe 405 410 Arg Asn Glu Ala Asn Asn Gln Glu Pro Phe Trp Leu His Ser Gly Lys 425 Ara

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<400> 472

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Lys Ser Thr Trp Val Thr Pro Ser Ala Glu Ala Ala Ala Glu Val Asn · 485 490 Ala His Leu Thr Ala Pro Leu Ser Arg Glu Ala Ser Gly Glu Asp Leu 505 Leu Arg Arg Pro Glu Met Thr Tyr Glu Lys Leu Thr Thr Leu Thr Pro 520 Phe Ala Pro Ala Leu Thr Asp Glu Gln Ala Ala Glu Gln Val Glu Ile 535 Gln Val Lys Tyr Glu Gly Tyr Ile Ala Arg Gln Gln Asp Glu Ile Glu 550 555 Lys Gln Leu Arg Asn Glu Asn Thr Leu Leu Pro Ala Thr Leu Asp Tyr 570 Arg Gln Val Ser Gly Leu Ser Asn Glu Val Ile Ala Lys Leu Asn Asp 585 His Lys Pro Ala Ser Ile Gly Gln Ala Ser Arg Ile Ser Gly Val Thr 600 Pro Ala Ala Ile Ser Ile Leu Leu Val Trp Leu Lys Lys Gln Gly Met Leu Arg Arg Ser Ala

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### <400> 475

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 5
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 15

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 30

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Phe Thr Leu Arg Lys Gly Glu Ile Leu Gly Val Ser Gly Leu Met Gly 275 280 285
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250

Lys Leu Glu Asp Gln Tyr Pro His Leu Asp Lys Ala Pro Gly Asp Ile

Arg Leu Lys Val Asp Asn Leu Cys Gly Pro Gly Val Asn Asp Val Ser 260 265 270

230

235

Thr Ser Gly Tyr Val Thr Leu Asp Gly His Glu Val Val Thr Arg Ser 310 315 Pro Gin Asp Gly Leu Ala Asn Gly Ile Val Tyr Ile Ser Glu Asp Arg 330 325 Lys Arg Asp Gly Leu Val Leu Gly Met Ser Val Lys Glu Asn Met Ser 345 Leu Thr Ala Leu Arg Tyr Phe Ser Arg Ala Gly Gly Ser Leu Lys His 360 Ala Asp Glu Gln Gln Ala Val Ser Asp Phe Ile Arg Leu Phe Asn Val 375 380 Lys Thr Pro Ser Met Glu Gln Ala Ile Gly Leu Leu Ser Gly Gly Asn 395 390 Gln Gln Lys Val Ala Ile Ala Arg Gly Leu Met Thr Arg Pro Lys Val 405 . 410 Leu Ile Leu Asp Glu Pro Thr Arg Gly Val Asp Val Gly Ala Lys Lys 420 425 Glu Ile Tyr Gln Leu Ile Asn Gln Phe Lys Ala Asp Gly Leu Ser Ile 435 440 Ile Leu Val Ser Ser Glu Met Pro Glu Val Leu Gly Met Ser Asp Arg 460 455 Ile Ile Val Met His Glu Gly His Leu Ser Gly Glu Phe Thr Arg Glu 465 470 475 Gln Ala Thr Gln Glu Val Leu Met Ala Ala Ala Val Gly Lys Leu Asn 490 495 485 Arg Val Asn Gln Glu 500

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<212> PRT

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Val Ala Ala Gly Arg Ser Gly Ala Asn Ile Ala Phe Ile Ala Cys Thr
                       55
Gly Asp Asp Ser Ile Gly Glu Ser Val Arg Gln Gln Leu Ala Thr Asp
                   70
                                       75
Asn Ile Asp Ile Thr Pro Val Ser Val Ile Lys Gly Glu Ser Thr Gly
                                   90
Val Ala Leu Ile Phe Val Asn Gly Glu Gly Glu Asn Val Ile Gly Ile
                              105
His Ala Gly Ala Asn Ala Ala Leu Ser Pro Ala Leu Val Glu Ala Gln
                           120
Arg Glu Arg Ile Ala Asn Ala Ser Ala Leu Leu Met Gln Leu Glu Ser
                      135
                                           140
Pro Leu Glu Ser Val Met Ala Ala Ala Lys Ile Ala His Gln Asn Lys
                                       155
                   150
Thr Ile Val Ala Leu Asn Pro Ala Pro Ala Arg Glu Leu Pro Asp Glu
                                    170
Leu Leu Ala Leu Val Asp Ile Ile Thr Pro Asn Glu Thr Glu Ala Glu
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Lys Leu Thr Gly Ile Arg Val Glu Asn Asp Glu Asp Ala Ala Lys Ala
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Ala Gln Val Leu His Glu Lys Gly Ile Arg Thr Val Leu Ile Thr Leu
                        215
Gly Ser Arg Gly Val Trp Ala Ser Val Asn Gly Glu Gly Gln Arg Val
                   230
                                       235
Pro Gly Phe Arg Val Gln Ala Val Asp Thr Ile Ala Ala Gly Asp Thr
Phe Asn Gly Ala Leu Ile Thr Ala Leu Leu Glu Glu Lys Pro Leu Pro
                                265
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-486-

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(54) Title: GENES IDENTIFIED AS REQUIRED FOR PROLIFERATION OF E. COLI

(57) Abstract: The sequences of nucleic acids encoding proteins required for E. coli proliferation are disclosed. The nucleic acids can also be used to screen for homologous genes that are required for proliferation in microorganisms other than E. coli. The nucleic acids can also be used to design expression vectors and secretion vectors. The nucleic acids can be used to express proteins or portions thereof, to obtain antibodies capable of specifically binding to the expressed proteins, and to use those expressed proteins as a screen to isolate candidate molecules for rational drug discovery programs. The nucleic acids of the present invention can also be used in various assay systems to screen for antimicrobial agents.

## AMENDED CLAIMS

[received by the International Bureau on 14 January 2002 (14.01.02); original claims 1-131 replaced by amended claims 1-131 (14 pages)]

- 1. A purified or isolated nucleic acid sequence consisting essentially of one the sequence of nucleotides of SEQ ID NOs: 1-93, wherein expression of said nucleic acid in a microorganism is capable of inhibiting proliferation of a microorganism.
- 2. The nucleic acid sequence of Claim 1, wherein said nucleic acid sequence is complementary to at least a portion of the nucleotide sequence of the coding strand of a gene whose expression is required for proliferation of a microorganism.
- 3. The nucleic acid of Claim 1, wherein said nucleic acid sequence has a nucleotide sequence complementary to at least a portion of the nucleotide sequence of an RNA required for proliferation of a microorganism.
- 4. The nucleic acid of Claim 3, wherein the nucleotide sequence of said RNA encodes more than one gene product.
- 5. A purified or isolated nucleic acid comprising a fragment of one of the nucleotide seuqence of SEQ ID NOs.: 1-93, said fragment selected from the group consisting of fragments comprising at least 10, at least 20, at least 25, at least 30, at least 50 and more than 50 consecutive nucleotides of one of the nucleotide sequences of SEQ ID NOs: 1-93.
- 6. A vector comprising a promoter operably linked to the nucleic acid sequence of Claims 1,2,3,4, or 5.
- 7. The vector of Claim 6, wherein said promoter is active in a microorganism selected from the group consisting of Aspergillus fumigatus, Bacillus anthracis, Burkholderia cepacia, Campylobacter jejuni, Candida albicans, Candida glabrata (also called Torulopsis glabrata), Candida tropicalis, Candida parapsilosis, Candida guilliermondii, Candida krusei, Candida kefyr (also called Candida pseudotropicalis), Candida dubliniensis, Chlamydia pneumoniae, Chlamydia trachomatus, Clostridium botulinum, Clostridium difficile, Cryptococcus neoformans, Enterobacter cloacae, Enterococcus faecalis, Escherichia coli, Haemophilus influenzae, Helicobacter pylori, Klebsiella pneumoniae, Listeria monocytogenes, Mycobacterium leprae, Mycobacterium tuberculosis, Neisseria gonorrhoeae, Pseudomonas aeruginosa, Salmonella cholerasuis, Salmonella enterica, Salmonella paratyphi, Salmonella typhi, Salmonella typhimurium, Staphylococcus aureus, Klebsiella pneumoniae, Listeria monocytogenes, Moxarella catarrhalis, Shigella boydii, Shigella dysenteriae, Shigella flexneri, Shigella sonnei, Pseudomonas aeruginosa, Staphylococcus epidermidis, Streptococcus pneumoniae, Treponema pallidum, Yersinia pestis and any species falling within the genera of any of the above species.
  - 8. A host cell containing the vector of Claim 6.
- 9. A purified or isolated nucleic acid consisting essentially of the coding sequence of one of SEQ ID NOs: 105-112, 119-122, 134-160, 164-171, 179-265, 271-273, 275, and 279-286.

10. A fragment of the nucleic acid of Claim 8, said fragment comprising at least 10, at least 20, at least 25, at least 30, at least 50 or more than 50 consecutive nucleotides of one of SEQ ID NOs: 105-112, 119-122, 134-160, 164-171, 179-265, 271-273, 275, and 279-286.

- 11. A vector comprising a promoter operably linked to the nucleic acid of Claim 9 or Claim 10.
- 12. A purified or isolated antisense nucleic acid comprising a nucleic acid sequence complementary to at least a portion of an intragenic sequence, intergenic sequence, sequences spanning at least a portion of two or more genes, 5' noncoding region, or 3' noncoding region within an operon comprising a proliferation-required gene whose activity or expression is inhibited by an antisense nucleic acid comprising one of SEQ ID NOs.: 1-93.
- 13. A purified or isolated nucleic acid comprising a nucleic acid having at least 70% identity to a sequence selected from the group consisting of SEQ ID NOs.: 1-93, fragments comprising at least 25 consecutive nucleotides of SEQ ID NOs.: 1-93, the sequences complementary to SEQ ID NOs.: 1-93 and the sequences complementary to fragments comprising at least 25 consecutive nucleotides of SEQ ID NOs.: 1-93 as determined using BLASTN version 2.0 with the default parameters.
- 14. The nucleic acid of Claim 13, wherein said nucleic acid is from an organism selected from the group consisting of Aspergillus fumigatus, Bacillus anthracis, Burkholderia cepacia, Campylobacter jejuni, Candida albicans, Candida glabrata (also called Torulopsis glabrata), Candida tropicalis, Candida parapsilosis, Candida guilliermondii, Candida krusei, Candida kefyr (also called Candida pseudotropicalis), Candida dubliniensis, Chlamydia pneumoniae, Chlamydia trachomatus, Clostridium botulinum, Clostridium difficile, Cryptococcus neoformans, Enterobacter cloacae, Enterococcus faecalis, Escherichia coli, Haemophilus influenzae, Helicobacter pylori, Klebsiella pneumoniae, Listeria monocytogenes, Mycobacterium leprae, Mycobacterium tuberculosis, Neisseria gonorrhoeae, Pseudomonas aeruginosa, Salmonella cholerasuis, Salmonella enterica, Salmonella paratyphi, Salmonella typhi, Salmonella typhimurium, Staphylococcus aureus, Klebsiella pneumoniae, Listeria monocytogenes, Moxarella catarrhalis, Shigella boydii, Shigella dysenteriae, Shigella flexneri, Shigella sonnei, Pseudomonas aeruginosa, Staphylococcus epidermidis, Streptococcus pneumoniae, Treponema pallidum, Yersinia pestis and any species falling within the genera of any of the above species.
- 15. A vector comprising a promoter operably linked to a nucleic acid encoding a polypeptide whose expression is inhibited by an antisense nucleic acid comprising one of SEQ ID NOs.: 1-93.
  - 16. A host cell containing the vector of Claim 15.
  - 17. The vector of Claim 15, wherein said polypeptide comprises a polypeptide

comprising a sequence selected from the group consisting of SEQ ID NOs: 298-305, 312-315, 327-353, 357-364, 372-458, 464-466, 468 and 472-479.

- 18. A purified or isolated polypeptide comprising a polypeptide whose expression is inhibited by an antisense nucleic acid comprising one of SEQ ID NOs.: 1-93, or a fragment selected from the group consisting of fragments comprising at least 5, at least 10, at least 20, at least 30, at least 40, at least 50, at least 60 or more than 60 consecutive amino acids of one of the said polypeptides.
- 19. The polypeptide of Claim 18, wherein said polypeptide comprises a polypeptide comprising one of SEQ ID NOs.: 298-305, 312-315, 327-353, 357-364, 372-458, 464-466, 468 and 472-479 or a fragment comprising at least 5, at least 10, at least 20, at least 30, at least 40, at least 50, at least 60 or more than 60 consecutive amino acids of a polypeptide comprising a sequence selected from the group consisting of SEQ ID NOs.: 298-305, 312-315, 327-353, 357-364, 372-458, 464-466, 468 and 472-479.
- 20. A purified or isolated polypeptide comprising a polypeptide having at least 25% identity to a polypeptide whose expression is inhibited by a sequence selected from the group consisting of SEQ ID NOs.: 1-93, or at least 25% identity to a fragment comprising at least 5, at least 10, at least 20, at least 30, at least 40, at least 50, at least 60 or more than 60 consecutive amino acids of a polypeptide whose expression is inhibited by a nucleic acid selected from the group consisting of SEO ID NOs.: 1-93 as determined using FASTA version 3.0t78 with the default parameters.
- 21. The polypeptide of Claim 20, wherein said polypeptide has at least 25% identity to a polypeptide comprising one of SEQ ID NOs: 298-305, 312-315, 327-353, 357-364, 372-458, 464-466, 468 and 472-479 or at least 25% identity to a fragment comprising at least 5, at least 10, at least 20, at least 30, at least 40, at least 50, at least 60 or more than 60 consecutive amino acids of a polypeptide comprising one of SEQ ID NOs.: 298-305, 312-315, 327-353, 357-364, 372-458, 464-466, 468 and 472-479 as determined using FASTA version 3.0t78 with the default parameters.
  - 22. An antibody capable of specifically binding the polypeptide of one of Claims 18-21.
- 23. A method of producing a polypeptide, comprising introducing a vector comprising a promoter operably linked to a nucleic acid encoding a polypeptide whose expression is inhibited by an antisense nucleic acid comprising one of SEQ ID NOs.: 1-93 into a cell and expressing said polypeptide.
  - 24. The method of Claim 23, further comprising the step of isolating said polypeptide.
- 25. The method of Claim 23, wherein said polypeptide comprises a sequence selected from the group consisting of SEQ ID NOs.: 298-305, 312-315, 327-353, 357-364, 372-458, 464-466, 468 and 472-479.
  - 26. A method of inhibiting proliferation of a microorganism comprising inhibiting the

activity or reducing the amount of a gene product whose expression is inhibited by an antisense nucleic acid comprising a sequence selected from the group consisting of SEQ ID NOs.: 1-93 or inhibiting the activity or reducing the amount of a nucleic acid encoding said gene product.

- 27. The method of Claim 26, wherein said gene product comprises a polypeptide comprising a sequence selected from the group consisting of SEQ ID NOs.: 298-305, 312-315, 327-353, 357-364, 372-458, 464-466, 468 and 472-479.
- 28. A method for identifying a compound which influences the activity of a gene product required for proliferation, said gene product comprising a gene product whose expression is inhibited by an antisense nucleic acid comprising a sequence selected from the group consisting of SEQ ID NOs.: 1-93, said method comprising:

contacting said gene product with a candidate compound; and determining whether said compound influences the activity of said gene product.

- 29. The method of Claim 28, wherein said gene product is a polypeptide and said activity is an enzymatic activity.
- ÷ 30. The method of Claim 28, wherein said gene product is a polypeptide and said activity is a carbon compound catabolism activity.
- 31. The method of Claim 28, wherein said gene product is a polypeptide and said activity is a biosynthetic activity.
- 32. The method of Claim 28, wherein said gene product is a polypeptide and said activity is a transporter activity.
- 33. The method of Claim 28, wherein said gene product is a polypeptide and said activity is a transcriptional activity.
- 34. The method of Claim 28, wherein said gene product is a polypeptide and said activity is a DNA replication activity.
- 35. The method of Claim 28, wherein said gene product is a polypeptide and said activity is a cell division activity.
  - 36. A compound identified using the method of Claim 28.
- 37. The method of Claim 28, wherein said gene product is a polypeptide comprising a sequence selected from the group consisting of SEQ ID NOs.: 298-305, 312-315, 327-353, 357-364, 372-458, 464-466, 468 and 472-479.
- 38. A method for identifying a compound or nucleic acid having the ability to reduce the activity or level of a gene product required for proliferation, said gene product comprising a gene product whose activity or expression is inhibited by an antisense nucleic acid comprising a sequence selected from the group consisting of SEQ ID NOs.: 1-93, said method comprising:

(a) providing a target that is a gene or RNA, wherein said target comprises a nucleic acid encoding said gene product;

- (b) contacting said target with a candidate compound or nucleic acid; and
- (c) measuring an activity of said target.
- 39. The method of Claim 38, wherein said target is a messenger RNA molecule and said activity is translation of said messenger RNA.
- 40. The method of Claim 38, wherein said target is a messenger RNA molecule and said activity is transcription of a gene encoding said messenger RNA.
- 41. The method of Claim 38, wherein said target is a gene and said activity is transcription of said gene.
- 42. The method of Claim 38, wherein said target is a nontranslated RNA and said activity is processing or folding of said nontranslated RNA or assembly of said nontranslated RNA into a protein/RNA complex.
- 43. The method of Claim 38, wherein said target gene or RNA encodes a polypeptide comprising a sequence selected from the group consisting of SEQ ID NOs.: 298-305, 312-315, 327-353, 357-364, 372-458, 464-466, 468 and 472-479.
  - 44. A compound or nucleic acid identified using the method of Claim 38.
- 45. A method for identifying a compound which reduces the activity or level of a gene product required for proliferation of a microorganism, wherein the activity or expression of said gene product is inhibited by an antisense nucleic acid comprising a sequence selected from the group consisting of SEQ ID NOs.: 1-93, said method comprising the steps of:
  - (a) expressing a sub-lethal level of an antisense nucleic acid complementary to a nucleic acid encoding said gene product in a cell to reduce the activity or amount of said gene product in said cell, thereby producing a sensitized cell;
    - (b) contacting said sensitized cell with a compound; and
  - (c) determining whether said compound inhibits the growth of said sensitized cell.
- 46. The method of Claim 45, wherein said determining step comprises determining whether said compound inhibits the growth of said sensitized cell to a greater extent than said compound inhibits the growth of a nonsensitized cell.
- 47. The method of Claim 45, wherein said cell is selected from the group consisting of bacterial cells, fungal cells, plant cells, and animal cells.
  - 48. The method of Claim 45, wherein said cell is a Gram negative bacterium.
  - 49. The method of Claim 45, wherein said cell is an E. coli cell.
  - 50. The method of Claim 45, wherein said cell is from an organism selected from the

group consisting of Aspergillus furnigatus, Bacillus anthracis, Burkholderia cepacia, Campylobacter jejuni, Candida albicans, Candida glabrata (also called Torulopsis glabrata), Candida tropicalis, Candida parapsilosis, Candida guilliermondii, Candida krusei, Candida kefyr (also called Candida pseudotropicalis), Candida dubliniensis. Chlamydia pneumoniae, Chlamydia trachomatus, Clostridium botulinum, Clostridium difficile, Cryptococcus neoformans, Enterobacter cloacae, Enterococcus faecalis, Escherichia coli, Haemophilus influenzae, Helicobacter pylori, Klebsiella pneumoniae, Listeria monocytogenes, Mycobacterium leprae, Mycobacterium tuberculosis, Neisseria gonorrhoeae, Pseudomonas aeruginosa, Salmonella cholerasuis, Salmonella enterica, Salmonella paratyphi, Salmonella typhi, Salmonella typhimurium, Staphylococcus aureus, Klebsiella pneumoniae, Listeria monocytogenes, Moxarella catarrhalis, Shigella boydii, Shigella dysenteriae, Shigella flexneri, Shigella sonnei, Pseudomonas aeruginosa, Staphylococcus epidermidis, Streptococcus pneumoniae, Treponema pallidum, Yersinia pestis and any species falling within the genera of any of the above species.

- 51. The method of Claim 45, wherein said antisense nucleic acid is transcribed from an inducible promoter.
- 52. The method of Claim 51, further comprising the step of contacting said cell with a concentration of inducer which induces said antisense nucleic acid to a sub-lethal level.
- 53. The method of Claim 45, wherein growth inhibition is measured by monitoring optical density of a culture growth solution.
  - 54. The method of Claim 45, wherein said gene product is a polypeptide.
- 55. The method of Claim 54, wherein said polypeptide comprises a sequence selected from the group consisting of SEQ ID NOs.: 298-305, 312-315, 327-353, 357-364, 372-458, 464-466, 468 and 472-479.
  - 56. The method of Claim 45, wherein said gene product is an RNA.
  - 57. A compound identified using the method of Claim 45.
- 58. A method for inhibiting cellular proliferation comprising introducing a compound with activity against a gene whose activity or expression is inhibited by an antisense nucleic acid comprising a sequence selected from the group consisting of SEQ ID NOs.: 1-93 or a compound with activity against the product of said gene into a population of cells expressing said gene.
- 59. The method of Claim 58, wherein said compound is an antisense nucleic acid comprising a sequence selected from the group consisting of SEQ ID NOs.: 1-93, or a proliferation-inhibiting portion thereof.
- 60. The method of Claim 59, wherein said proliferation inhibiting portion of one of SEQ ID NOs.: 1-93 is a fragment comprising at least 10, at least 20, at least 25, at least 30, at least 50 or more than 51 consecutive nucleotides of one of SEQ ID NOs.: 1-93.

61. The method of Claim 58, wherein said population is a population selected from the group consisting of bacterial cells, fungal cells, plant cells, and animal cells.

- 62. The method of Claim 58, wherein said population is a population of Gram negative bacteria.
  - 63. The method of Claim 58, wherein said population is a population of *E. coli* cells.
- 64. The method of Claim 58, wherein said population is a population selected from the group consisting of Aspergillus fumigatus. Bacillus anthracis, Burkholderia cepacia, Campylobacter jejuni, Candida albicans, Candida glabrata (also called Torulopsis glabrata), Candida tropicalis, Candida parapsilosis, Candida guilliermondii, Candida krusei, Candida kefyr (also called Candida pseudotropicalis), Candida dubliniensis. Chlamydia pneumoniae, Chlamydia trachomatus, Clostridium botulinum, Clostridium difficile, Cryptococcus neoformans, Enterobacter cloacae, Enterococcus faecalis, Escherichia coli. Haemophilus influenzae, Helicobacter pylori, Klebsiella pneumoniae, Listeria monocytogenes. Mycobacterium leprae, Mycobacterium tuberculosis, Neisseria gonorrhoeae, Pseudomonas aeruginosa. Salmonella cholerasuis, Salmonella enterica, Salmonella paratyphi, Salmonella typhi. Salmonella typhimurium. Staphylococcus aureus, Klebsiella pneumoniae, Listeria monocytogenes. Moxarella catarrhalis, Shigella boydii, Shigella dysenteriae, Shigella flexneri, Shigella sonnei. Pseudomonas aeruginosa. Staphylococcus epidermidis, Streptococcus pneumoniae, Treponema pallidum, Yersinia pestis and any species falling within the genera of any of the above species.
- 65. The method of Claim 58, wherein said gene encodes a polypeptide comprising a sequence selected from the group consisting of SEQ ID NOs.: 298-305, 312-315, 327-353, 357-364, 372-458, 464-466, 468 and 472-479.
- 66. A preparation comprising an effective concentration of an antisense nucleic acid comprising a sequence selected from the group consisting of SEQ ID NOs.: 1-93, or a proliferation-inhibiting portion thereof in a pharmaceutically acceptable carrier.
- 67. The preparation of Claim 66, wherein said proliferation-inhibiting portion of one of SEQ ID NOs.: 1-93 comprises at least 10, at least 20, at least 25, at least 30, at least 50 or more than 50 consecutive nucleotides of one of SEQ ID NOs.: 1-93.
- 68. A method for inhibiting the activity or expression of a gene in an operon required for proliferation wherein the activity or expression of at least one gene in said operon is inhibited by an antisense nucleic acid comprising a sequence selected from the group consisting of SEQ ID NOs.: 1-93, said method comprising contacting a cell in a cell population with an antisense nucleic acid comprising at least a proliferation-inhibiting portion of said operon.
- 69. The method of Claim 68, wherein said antisense nucleic acid comprises a sequence selected from the group consisting of SEQ ID NOs.: 1-93 or a proliferation inhibiting portion thereof.

70. The method of Claim 68, wherein said cell is contacted with said antisense nucleic acid by introducing a plasmid which expresses said antisense nucleic acid into said cell population.

- 71. The method of Claim 68, wherein said cell is contacted with said antisense nucleic acid by introducing a phage which expresses said antisense nucleic acid into said cell population.
- 72. The method of Claim 68, wherein said cell is contacted with said antisense nucleic acid by expressing said antisense nucleic acid from the chromosome of cells in said cell population.
- 73. The method of Claim 68, wherein said cell is contacted with said antisense nucleic acid by introducing a promoter adjacent to a chromosomal copy of said antisense nucleic acid such that said promoter directs the synthesis of said antisense nucleic acid.
- 74. The method of Claim 68, wherein said cell is contacted with said antisense nucleic acid by introducing a retron which expresses said antisense nucleic acid into said cell population.
- 75. The method of Claim 68, wherein said cell is contacted with said antisense nucleic acid by introducing a ribozyme into said cell-population, wherein a binding portion of said ribozyme is complementary to said antisense oligonucleotide.
- 76. The method of Claim 68, wherein said cell is contacted with said antisense nucleic acid by introducing a liposome comprising said antisense oligonucleotide into said cell.
- 77. The method of Claim 68, wherein said cell is contacted with said antisense nucleic acid by electroporation of said antisense nucleic acid.
- 78. The method of Claim 68, wherein said antisense nucleic acid is a fragment comprising at least 10, at least 20, at least 25, at least 30. at least 50 or more than 50 consecutive nucleotides of one of SEQ ID NOs.: 1-93.
  - 79. The method of Claim 68 wherein said antisense nucleic acid is an oligonucleotide.
- 80. A method for identifying a gene which is required for proliferation of a microorganism comprising:
  - (a) contacting a microorganism other than E. coli with a nucleic acid selected from the group consisting of SEQ ID NOs.: 1-93:
  - (b) determining whether said nucleic acid inhibits proliferation of said microorganism; and
  - (c) identifying the gene in said microorganism which is inhibited by said nucleic acid.
  - 81. The method of Claim 80, wherein said microorganism is a Gram negative bacterium.
- 82. The method of Claim 80 wherein said microorganism is selected from the group consisting of Aspergillus fumigatus, Bacillus anthracis, Burkholderia cepacia, Campylobacter jejuni, Candida albicans, Candida glabrata (also called Torulopsis glabrata), Candida tropicalis, Candida parapsilosis, Candida guilliermondii, Candida krusei, Candida kefyr (also called Candida

pseudotropicalis), Candida dubliniensis, Chlamydia pneumoniae, Chlamydia trachomatus, Clostridium botulinum, Clostridium difficile, Cryptococcus neoformans, Enterobacter cloacae, Enterococcus faecalis, Escherichia coli, Haemophilus influenzae, Helicobacter pylori, Klebsiella pneumoniae, Listeria monocytogenes, Mycobacterium leprae, Mycobacterium tuberculosis, Neisseria gonorrhoeae, Pseudomonas aeruginosa, Salmonella cholerasuis, Salmonella enterica, Salmonella paratyphi, Salmonella typhi, Salmonella typhimurium, Staphylococcus aureus, Klebsiella pneumoniae, Listeria monocytogenes, Moxarella catarrhalis, Shigella boydii, Shigella dysenteriae, Shigella flexneri, Shigella sonnei. Pseudomonas aeruginosa, Staphylococcus epidermidis, Streptococcus pneumoniae, Treponema pallidum, Yersinia pestis and any species falling within the genera of any of the above species.

- 83. The method of Claim 80, further comprising introducing said nucleic acid into a vector functional in said microorganism prior to introducing said inhibitory nucleic acid into said microorganism.
- 84. A method for identifying a compound having the ability to inhibit proliferation of a microorganism comprising:
  - (a) identifying in a first microorganism a homolog of a gene or gene product present in a second microorganism which is different than said first microorganism, wherein the activity or level of said gene or gene product is inhibited by a nucleic acid comprising a sequence selected from the group consisting of SEQ ID NOs. 1-93;
  - (b) identifying an inhibitory nucleic acid sequence which inhibits the activity of said homolog in said first microorganism;
  - (c) contacting said first microorganism with a sub-lethal level of said inhibitory nucleic acid, thus sensitizing said first microorganism:
    - (d) contacting the sensitized microorganism of step (c) with a compound; and
  - (e) determining whether said compound inhibits proliferation of said sensitized microorganism.
- 85. The method of Claim 84, wherein said determining step comprises determining whether said compound inhibits proliferation of said sensitized microorganism to a greater extent than said compound inhibits proliferation of a nonsensitized microorganism.
- 86. The method of Claim 84 wherein step (a) comprises identifying a homologous nucleic acid to a gene or gene product whose activity or level is inhibited by a nucleic acid selected from the group consisting of SEQ ID NOs. 1-93 or a nucleic acid encoding a homologous polypeptide to a polypeptide whose activity or level is inhibited by a nucleic acid selected from the group consisting of SEQ ID NOs. 1-93 by using an algorithm selected from the group consisting of BLASTN version 2.0 with the default parameters and FASTA version 3.0t78 algorithm with the

default parameters to identify said homologous nucleic acid or said nucleic acid encoding a homologous polypeptide in a database.

- 87. The method of Claim 84 wherein said step (a) comprises identifying a homologous nucleic acid or a nucleic acid encoding a homologous polypeptide by identifying nucleic acids which hybridize to said first gene.
- 88. The method of Claim 84 wherein the step (a) comprises expressing a nucleic acid selected from the group consisting of SEQ ID NOs. 1-93 in said microorganism.
- 89. The method of Claim 84, wherein said inhibitory nucleic acid is an antisense nucleic acid.
- 90. The method of Claim 84, wherein said inhibitory nucleic acid comprises an antisense nucleic acid to a portion of said homolog.
- 91. The method of Claim 84, wherein said inhibitory nucleic acid comprises an antisense nucleic acid to a portion of the operon encoding said homolog.
- 92. The method of Claim 84, wherein the step of contacting the first microorganism with a sub-lethal level of said inhibitory nucleic acid comprises directly contacting said microorganism with said inhibitory nucleic acid.
- 93. The method of Claim 84, wherein the step of contacting the first microorganism with a sub-lethal level of said inhibitory nucleic acid comprises expressing an antisense nucleic acid to said homolog in said microorganism.
- 94. The method of Claim 84, wherein said gene product comprises a polypeptide comprising a sequence selected from the group consisting of SEQ ID NOs.: 298-305, 312-315, 327-353, 357-364, 372-458, 464-466, 468 and 472-479.
  - A compound identified using the method of Claim 84.
- 96. A method of identifying a compound having the ability to inhibit proliferation comprising:
  - (a) contacting a microorganism other than *E. coli* with a sub-lethal level of a nucleic acid comprising a sequence selected from the group consisting of SEQ ID NOs. 1-93 or a portion thereof which inhibits the proliferation of *E. coli*, thus sensitizing said microorganism;
    - (b) contacting the sensitized microorganism of step (a) with a compound; and
  - (c) determining whether said compound inhibits proliferation of said sensitized microorganism.
- 97. The method of Claim 96, wherein said determining step comprises determining whether said compound inhibits proliferation of said sensitized microorganism to a greater extent than said compound inhibits proliferation of a nonsensitized microorganism.

- 98. A compound identified using the method of Claim 96.
- 99. A method for identifying a compound having activity against a biological pathway required for proliferation comprising:
  - (a) sensitizing a cell by expressing a sub-lethal level of an antisense nucleic acid complementary to a nucleic acid encoding a gene product required for proliferation, wherein the activity or expression of said gene product is inhibited by an antisense nucleic acid comprising a sequence selected from the group consisting of SEQ ID NOs.: 1-93, in said cell to reduce the activity or amount of said gene product;
    - (b) contacting the sensitized cell with a compound; and
  - (c) determining whether said compound inhibits the growth of said sensitized cell.
- 100. The method of Claim 99, wherein said determining step comprises determining whether said compound inhibits the growth of said sensitized cell to a greater extent than said compound inhibits the growth of a nonsensitized cell.
- 101. The method of Claim 99, wherein said cell is selected from the group consisting of bacterial cells, fungal cells, plant cells, and animal cells.
  - 102. The method of Claim 99, wherein said cell is a Gram negative bacterium.
  - 103. The method of Claim 99, wherein said Gram negative bacterium is E. coli.
- Aspergillus fumigatus, Bacillus anthracis. Burkholderia cepacia. Campylobacter jejuni, Candida albicans, Candida glabrata (also called Torulopsis glabrata). Candida tropicalis, Candida parapsilosis, Candida guilliermondii, Candida krusei, Candida kefyr (also called Candida pseudotropicalis), Candida dubliniensis, Chlamydia pneumoniae, Chlamydia trachomatus, Clostridium botulinum, Clostridium difficile, Cryptococcus neoformans, Enterobacter cloacae, Enterococcus faecalis, Escherichia coli, Haemophilus influenzae. Helicobacter pylori, Klebsiella pneumoniae, Listeria monocytogenes, Mycobacterium leprae, Mycobacterium tuberculosis, Neisseria gonorrhoeae, Pseudomonas aeruginosa, Salmonella cholerasuis, Salmonella enterica, Salmonella paratyphi, Salmonella typhi, Salmonella typhimurium, Staphylococcus aureus, Klebsiella pneumoniae, Listeria monocytogenes, Moxarella catarrhalis, Shigella boydii, Shigella dysenteriae, Shigella flexneri, Shigella sonnei, Pseudomonas aeruginosa, Staphylococcus epidermidis, Streptococcus pneumoniae, Treponema pallidum, Yersinia pestis and any species falling within the genera of any of the above species.
- 105. The method of Claim 99, wherein said antisense nucleic acid is transcribed from an inducible promoter.
  - 106. The method of Claim 99, further comprising contacting the cell with an agent which

induces expression of said antisense nucleic acid from said inducible promoter, wherein said antisense nucleic acid is expressed at a sub-lethal level.

- 107. The method of Claim 99, wherein inhibition of proliferation is measured by monitoring the optical density of a liquid culture.
- 108. The method of Claim 99, wherein said gene product comprises a polypeptide comprising a sequence selected from the group consisting of SEQ ID NOs.: 298-305, 312-315, 327-353, 357-364, 372-458, 464-466, 468 and 472-479
  - 109. A compound identified using the method of Claim 99.
- 110. A method for identifying a compound having the ability to inhibit cellular proliferation comprising:
  - (a) contacting a cell with an agent which reduces the activity or level of a gene product required for proliferation of said cell, wherein said gene product is a gene product whose activity or expression is inhibited by an antisense nucleic acid comprising a sequence selected from the group consisting of SEQ ID NOs.: 1-93;
    - (b) contacting said cell with a compound; and
    - (c) determining whether said compound reduces proliferation of said contacted cell.
- 111. The method of Claim 110, wherein said determining step comprises determining whether said compound reduces proliferation of said contacted cell to a greater extent than said compound reduces proliferation of cells which have not been contacted with said agent.
- 112. The method of Claim 110, wherein said agent which reduces the activity or level of a gene product required for proliferation of said cell comprises an antisense nucleic acid to a gene or operon required for proliferation.
- 113. The method of Claim 110, wherein said agent which reduces the activity or level of a gene product required for proliferation of said cell comprises a compound known to inhibit growth or proliferation of a microorganism.
- 114. The method of Claim 110, wherein said cell contains a mutation which reduces the activity or level of said gene product required for proliferation of said cell.
  - 115. The method of Claim 114, wherein said mutation is a temperature sensitive mutation.
- 116. The method of Claim 110, wherein said gene product comprises a polypeptide comprising a sequence selected from the group consisting of SEQ ID NOs.: 298-305, 312-315, 327-353, 357-364, 372-458, 464-466, 468 and 472-479
  - 117. A compound identified using the method of Claim 110.
- 118. A method for identifying the biological pathway in which a proliferation-required gene or its gene product lies, wherein said gene or gene product comprises a gene or gene product

whose activity or expression is inhibited by an antisense nucleic acid comprising a sequence selected from the group consisting of SEQ ID NOs.: 1-93, said method comprising:

- (a) expressing a sub-lethal level of an antisense nucleic acid which inhibits the activity of said proliferation-required gene or gene product in a cell;
- (b) contacting said cell with a compound known to inhibit growth or proliferation of a microorganism, wherein the biological pathway on which said compound acts is known; and
  - (c) determining whether said cell is sensitive to said compound.
- 119. The method of Claim 118, wherein said determining step comprises determining whether said cell has a substantially greater sensitivity to said compound than a cell which does not express said sub-lethal level of said antisense nucleic acid and wherein said gene or gene product lies in the same pathway on which said compound acts if said cell expressing said sub-lethal level of said antisense nucleic acid has a substantially greater sensitivity to said compound than said cell which does not express said sub-lethal level of said antisense nucleic acid.
- 120. The method of Claim 118, wherein said gene product comprises a polypeptide comprising a sequence selected from the group consisting of SEQ ID NOs.: 298-305, 312-315, 327-353, 357-364, 372-458, 464-466, 468 and 472-479
- 121. A method for determining the biological pathway on which a test compound acts comprising:
  - (a) expressing a sub-lethal level of an antisense nucleic acid complementary to a proliferation-required nucleic acid in a cell, wherein the activity or expression of said proliferation-required nucleic acid is inhibited by an antisense nucleic acid comprising a sequence selected from the group consisting of SEQ ID NOs.: 1-93 and wherein the biological pathway in which said proliferation-required nucleic acid or a protein encoded by said proliferation-required polypeptide lies is known.
    - (b) contacting said cell with said test compound; and
    - (c) determining whether said cell is sensitive to said test compound.
- 122. The method of Claim 121, wherein said determining step comprises determining whether said cell has a substantially greater sensitivity to said test compound than a cell which does not express said sub-lethal level of said antisense nucleic acid.
  - 123. The method of Claim 121, further comprising:
  - (d) expressing a sub-lethal level of a second antisense nucleic acid complementary to a second proliferation-required nucleic acid in a second cell, wherein said second proliferation-required nucleic acid is in a different biological pathway than said proliferation-required nucleic acid in step (a); and

(e) determining whether said second cell does not have a substantially greater sensitivity to said test compound than a cell which does not express said sub-lethal level of said second antisense nucleic acid, wherein said test compound is specific for the biological pathway against which the antisense nucleic acid of step (a) acts if said second cell does not have substantially greater sensitivity to said test compound.

- 124. A purified or isolated nucleic acid comprising a sequence selected from the group consisting of SEQ ID NOs.: 1-93.
- 125. A compound which interacts with a gene or gene product whose activity or expression is inhibited by an antisense nucleic acid comprising one of SEQ ID NOs.: 1-93 to inhibit proliferation.
- 126. A compound which interacts with a polypeptide whose expression is inhibited by an antisense nucleic acid comprising one of SEQ ID NOs.: 1-93 to inhibit proliferation.
  - 127. A method for manufacturing an antibiotic comprising the steps of:

    screening one or more candidate compounds to identify a compound that reduces
    the activity or level of a gene product required for proliferation, said gene product
    comprising a gene product whose activity or expression is inhibited by an antisense nucleic
    acid comprising a sequence selected from the group consisting of SEQ ID NOs.: 1-93; and
    manufacturing the compound so identified.
- 128. The method of Claim 127, wherein said screening step comprises performing any one of the methods of Claims 28, 38, 45, 96, 99 and 110.
- 129. A method for inhibiting proliferation of a microorganism in a subject comprising administering a compound that reduces the activity or level of a gene product required for proliferation of said microorganism, said gene product comprising a gene product whose activity or expression is inhibited by an antisense nucleic acid comprising a sequence selected from the group consisting of SEQ ID NOs.: 1-93 to said subject.
- 130. The method of Claim 129 wherein said subject is selected from the group consisting of vertebrates, mammals, avians, and human beings.
- 131. The method of Claim 129, wherein said gene product comprises a polypeptide comprising a sequence selected from the group consisting of SEQ ID NOs.: 298-305, 312-315, 327-353, 357-364, 372-458, 464-466, 468 and 472-479.

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(57) Abstract: The sequences of nucleic acids encoding proteins required for E. coli proliferation are disclosed. The nucleic acids can also be used to screen for homologous genes that are required for proliferation in microorganisms other than E. coli. The nucleic acids can also be used to design expression vectors and secretion vectors. The nucleic acids can be used to express proteins or portions thereof, to obtain antibodies capable of specifically binding to the expressed proteins, and to use those expressed proteins as a screen to isolate candidate molecules for rational drug discovery programs. The nucleic acids of the present invention can also be used in various assay systems to screen for antimicrobial agents.



#### P'TERNATIONAL SEARCH REPORT

Is attornal Application No PCT/US 00/34419

A. CLASSIFICATION OF SUBJECT MATTER IPC 7 C12N15/31 C12 C12N15/10 CO7K14/245 C12N15/11 According to International Patent Classification (IPC) or to both national classification and IPC B. FIELDS SEARCHED Minimum documentation searched (classification system followed by classification symbols) IPC 7 C12N C07K Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched Electronic data base consulted during the international search (name of data base and, where practical, search terms used) SEQUENCE SEARCH, EPO-Internal, WPI Data, PAJ, BIOSIS C. DOCUMENTS CONSIDERED TO BE RELEVANT Citation of document, with indication, where appropriate, of the relevant passages Relevant to claim No. Category * DATABASE EM_PRO 'Online! 5,10,13, X EMBL; 29 January 1997 (1997-01-29) 14, BLATTNER ET AL.: "Escherichia coli K12 18-21, MG1655 section 337 of 400 of the complete 124 genome" retrieved from EBI, accession no. ECAE447 Database accession no. AE000447 XP002181127 the whole document 1-131 -& DATABASE SWALL 'Online! 5,10,13, X 1 May 1992 (1992-05-01) 14, BURLAND ET AL.: "60 kDa inner-membrane 18-21, 124 protein" retrieved from EBI, accession no. 60IM_ECOLI Database accession no. P25714 XP002181128 the whole document -& DATABASE EM_PRO 'Online! 5,13,14, X -/--Further documents are listed in the continuation of box C. Patent family members are listed in annex. " Special categories of cited documents: *T* later document published after the international filing date or priority date and not in conflict with the application but "A" document defining the general state of the art which is not considered to be of particular relevance cited to understand the principle or theory underlying the invention "E" earlier document but published on or after the international "X" document of particular relevance; the claimed invention filing date cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such docu-*O* document referring to an oral disclosure, use, exhibition or ments, such combination being obvious to a person skilled other means *P* document published prior to the international filing date but later than the priority date claimed '&' document member of the same patent family Date of mailing of the international search report Date of the actual completion of the international search 3 0. 11. 01 15 November 2001 Authorized officer Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentlaan 2

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-& BLATTNER ET AL.: "THE COMPLETE GENOME SEQUENCE OF ESCHERICHIA COLI K-12" SCIENCE, vol. 277, 5 September 1997 (1997-09-05), pages 1453-1462, XP002923023 the whole document & THE JOURNAL OF BIOLOGICAL CHEMISTRY, vol. 273, no. 46, 13 November 1998 (1998-11-13), pages	1,9
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II atlanal Application No PCT/US 00/34419

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PCT/US 00/34419

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	ution) DOCUMENTS CONSIDERED TO BE RELEVANT		
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...ternational application No. PCT/US 00/34419

## INTERNATIONAL SEARCH REPORT

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)
This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:
1. X Claims Nos.:  because they relate to subject matter not required to be searched by this Authority, namely:  see FURTHER INFORMATION sheet PCT/ISA/210
2. X Claims Nos.:  Decause they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:  See FURTHER INFORMATION sheet PCT/ISA/210
3. Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).
Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)
This International Searching Authority found multiple Inventions in this international application, as follows:
see additional sheet
As a result of the prior review under R. 40.2(e) PCT, part of the additional fees are to be refunded.
As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable daims.
As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. X As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
1-131 (Seq. Id. Nos. 1, 60, 220 and 413)
4. No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:
Remark on Protest  X The additional search fees were accompanied by the applicant's protest.  No protest accompanied the payment of additional search fees.

### FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

#### Continuation of Box I.1

As far as claims 129-131 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

Continuation of Box I.I

Rule 39.1(iv) PCT - Method for treatment of the human or animal body by therapy

#### Continuation of Box I.2

Present claims 36, 44, 57, 95, 98, 109, and 117 relate to a compound defined by reference to a desirable characteristic or property, namely being identifiable by using the method of claims 28, 38, 45, 84, 96, 99, and 110, respectively. Present claims 125 and 126 relate to a compound defined by reference to a desirable characteristic or property, namely interacting with a gene or gene product or a polypeptide whose activity or expression is inhibited by an antisense nucleic acid comprising one of SEQ ID NOS 1-127.

The claims cover all compounds having this characteristic or property, whereas the application provides support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT for only a very limited number of such compounds. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Independent of the above reasoning, the claims also lack clarity (Article 6 PCT). An attempt is made to define the compound by reference to a result to be achieved. Again, this lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope impossible. Consequently, the search has been carried out for those parts of the claims which appear to be clear, supported and disclosed, namely those parts relating to the sequences of claims 1, 9 and 19.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

#### FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claims: 1-8, 12-14, 45-124, 129-131 all partially

Invention 1:

A purified or isolated nucleic acid sequence, consisting of Seq Id No 1, a vector comprising said sequence, a host cell containing said vector, and their uses.

2. Claims: 1-8, 12-14, 45-124, 129-131 all partially

Inventions 2 to 93:

Idem as invention 1, but for Seq Id Nos 2-93, respectively.

3. Claims: 9-11, 15-44, 125-128 all partially

Invention 94:

A purified or isolated nucleic acid sequence consisting of Seq Id No 106, a vector comprising said sequence, a host cell containing said vector, a polypeptide encoded by said nucleic acid sequence and having Seq Id No 299, and an antibody binding said polypeptide, and their uses.

4. Claims: 9-11, 15-44, 125-128 all partially

Inventions 95 to 231:

Idem as invention 94, but for nucleic acid Seq Id Nos 107-112, 119-122, 134-160, 164-171, 179-265, 271-273, 275, 279-286 and corresponding polypeptide Seq Id Nos 300-305, 312-315, 327-333, 357-364, 372-458, 464-466, 468, 472-479, respectively.

## PTERNATIONAL SEARCH REPORT

Information on patent family members

In .tlonal Application No PCT/US 00/34419

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